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OSTEOMALACIA OF UNKNOWN ETIOLOGY*

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OSTEOMALACIA is a generalized disease of bone characterized by lack of calcification of a presumably normal osteoid matrix. The chemical changes in the serum are usually diagnostic and consist of a normal or low serum calcium, a low or normal serum inorganic phosphorus and an elevated serum alkaline phosphatase. In all cases the product of the serum calcium and serum phosphorus is decreased.[1] Radiologically, there may be generalized decreased bony density or the isolated lines of decalcification (the "pseudofractures" first described by Looser[2]) or both.

The causes of osteomalacia can usually be determined readily. They may be classified into two groups: those in which ingested calcium or phosphorus is not absorbed from the gastrointestinal tract; and those in which there are unusually large losses of calcium or phosphorus in the urine.

Faulty calcium absorption is most frequently the result of vitamin D deficiency.[3] Thus, there may be an actual lack of vitamin D in the diet as in infantile rickets, or a failure to absorb vitamin D from the gastrointestinal tract as in steatorrhea. A rare condition, in which massive amounts of vitamin D are necessary for adequate calcium absorption, has been termed rickets resistant to vitamin D.[4]

Osteomalacia may result from excessive urinary losses of calcium and phosphorus as occurs in "tubular insufficiency without glomerular insufficiency",[5] idiopathic hypercalciuria and the Fanconi syndrome.[6] The osteomalacia in the case presented below cannot be attributed to any one of these causes. Although there were many features resembling those in the case of "raised resistance to vitamin D" reported by McCance[7] there were equally prominent dissimilarities.

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CASE REPORT

A 25-year-old Negro dated the onset of his illness to May, 1951, when he first experienced backache after a fall. In September of that year aching pain in the right foot and right ankle developed, and 4 months later the right knee and hip were similarly affected. At this time x-ray films of the hips, back and legs were reported as normal. In October, 1952, the patient suffered an accidental burn, which became secondarily infected and required hospitalization. During his convalescence, because the pain in the right knee became more severe, an arthrotomy was performed and a "joint mouse" was removed. Pain in the feet, knees and hips persisted, however, and x-ray examination in June, 1953, revealed pseudofractures of both tibias, the 1st metatarsals, the os calci and several ribs (Fig. 1). In the following month further x-ray studies showed the same picture, and a bone biopsy was performed at the site of a pseudofracture in the tibia (Fig. 2). The sections showed hypercellular bone with dense spicules but with normal architecture. Decalcification of the specimen was too complete to reveal osteoid. Syphilitic bone disease was considered because of a history of secondary syphilis, and this was further treated with 18,000,000 units of penicillin. The patient was then transferred to another hospital, where laboratory studies revealed a low serum phosphorus, hyperchloremia, a slightly reduced carbon dioxide combining power and hypocalciuria. There was decreased density of bone, particularly of the pelvis, lumbar vertebras and femurs, and the pseudofractures were again observed. An excretory urogram and small-bowel x-ray films were normal.

In April, 1954, the patient was transferred to Walter Reed Army Hospital with the diagnosis of osteomalacia of unknown etiology. Physical examination revealed none of the signs of infantile rickets. Except for mild muscle wasting and limitation of motion in the back and hips the examination was negative.

Initial studies revealed a low serum phosphorus ranging between 0.9 mg. and 1.2 mg. per 100 ml. The serum calcium was normal. The alkaline phosphatase ranged from 5 to 8 Bodansky units. The carbon dioxide content was between 21 and 25 milliequiv. per liter. There was no elevation of the blood urea nitrogen, and the urea clearance was normal. Previous x-ray findings were confirmed.

From May, 1954, to December, 1955, the patient was studied on the Metabolic Ward of Walter Reed Army Medical Center. Since February, 1955, he has received no less than 100,000 units of vitamin D_2 daily in addition to other medicaments. No therapeutic regimen has effected the remineralization of his bones. Intermittent pain in the feet, legs, hips and back has continued.

METHODS

All chemical determinations were done in the laboratory of the Department of Metabolism. Details of

these methods have been published.[8] The technics of certain studies are outlined here.

During all balance studies the patient was confined to the Metabolic Ward. A weighed solid diet and distilled water were used. Aliquots of the diet were analyzed one to three times a week and were consistent in their chemical composition. Stools and urine were collected in separate containers — forty-eight-hour urine collections and ninety-six-hour stool collections were obtained for these studies. Stool markers were used only for the final balance study. The patient was placed on the diet at least six days before each study to allow time for equilibration.

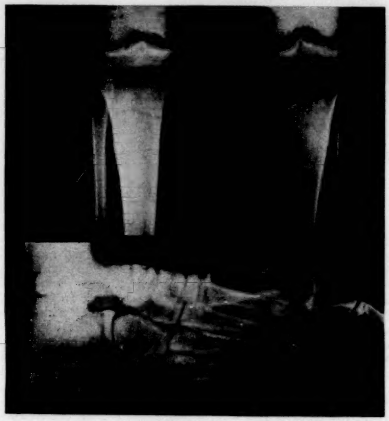

FIGURE 1. *Roentgenograms, Showing Pseudofractures in the Proximal End of Each Tibia, in the First Metatarsal and in the Os Calcaneus.*

Calcium infusions were given on several occasions; 10 mg. of calcium (as the gluconate) per kilogram of body weight was administered intravenously over a three-hour period after several days of equilibration on a constant calcium and phosphorus intake. Measurement of the changes in serum and urinary phosphorus were conducted as described by Howard et al.[9] Calcium retention was evaluated by comparison of the excretion on the test day with that noted before infusion.[10,11] Hourly samples of blood and urine obtained before, during and after the infusion were analyzed for phosphorus and creatinine, thus permitting calculation of changes in the filtration rate and in the tubular reabsorption of phosphorus.[12]

The phosphorus clearance was determined during all studies. The creatinine clearance was used, unless otherwise specified, to determine the glomerular filtration rate. This rate, in milliliters per minute, times the serum concentration of phosphorus gives the amount of phosphorus in milligrams filtered per minute. If the amount of phosphorus excreted per minute is subtracted from the amount filtered, the difference represents the number of milligrams reabsorbed by the renal tubules. The amount reabsorbed divided by the amount filtered gives the percentage of filtered phosphorus reabsorbed, 91 $\pm$ 3 per cent being considered normal.[13] The maximum reabsorptive capacity of the renal tubules for phosphorus was determined by the infusion of a solution containing 11.36 gm. of disodium phosphate and 2.76 gm. of monosodium phosphate per liter. The rate of infusion was increased each forty minutes. Total urine collections and a blood sample were obtained for each period.

RESULTS

The studies on this patient are presented chronologically so far as possible. Because hyperchloremia and a reduction of the carbon dioxide combining power had been observed at another hospital, atten-

TABLE 1. *Important Laboratory Findings.*

BONE AND MINERAL							URINE							
CALCIUM	PHOSPHORUS	ALKALINE PHOSPHATASE	CITRATE	X-RAY FINDINGS	BIOPSY FINDINGS	SUGAR	AMINO ACID EXCRETION	PHOSPHATE CLEARANCE	pH*	AMMONIA†	TITRATABLE ACID†	INULIN CLEARANCE	TUBULAR REABSORPTION OF GLUCOSE	CALCIUM EXCRETION	EXCRETORY UROGRAM
mg./100 ml.	*mg./100 ml.*	*Bodansky units*	*mg./100 ml.*				*mg./day*	*ml./min./1.73 sq. m.*		*gm./day*	*milliequiv./day*	*ml./min./1.73 sq. m.*	*mg./min./1.73 sq. m.*	*mg./day*	
10-12	0.9-1.2	5-11	1.2-1.7	"Osteoporosis"; pseudofractures.	"Noncalcified callus"	None	300-500	35	5.31-7.91	1.81‡	30.5	132	337	50	Normal

*Range.
†Maximum.
‡Equivalent of 130 milliequiv./day.

tion was first paid to the renal tubule. As shown in Table 1, there was no impairment of kidney function. Clearances, renal plasma flow and reabsorptive capacity for glucose were normal. There was no glycosuria or amino-aciduria. Ammonium chloride (150 milliequiv. per day) was given. By the fourth day the urinary ammonia had increased by 90 milliequiv. per

day, and the urinary titratable acid by 20 milliequiv. per day over control values. Urinary pH fell to 5.31. During these studies excretion of calcium was less than 50 mg. a day. After the completion of this study the blood pH was normal, but the carbon dioxide remained low. Impaired intestinal absorption of calcium could therefore be inferred, and attention was turned to the gastrointestinal tract. Reference again to Table 1 discloses that steatorrheal disease can be excluded with some confidence. The stool fat was not increased. Roentgenologic examination of the gastrointestinal tract was negative. Absorption of fat-soluble vitamins was satisfactory as revealed by a normal prothrombin time and a prompt and adequate rise in serum vitamin A content after the oral ingestion of a standard dose of vitamin A.

In September, 1954, the patient was placed on the first of four balance studies (Periods 1-6, Fig. 3) to evaluate absorption and retention of calcium and phosphorus. During the three periods before the administration of vitamin D_2 he was in calcium and phosphorus equilibrium; approximately 95 per cent of the ingested calcium, and 40 per cent of the ingested phosphorus was lost in the stool. He was placed on 100,000 units of vitamin D_2 a day. During the next twelve days there was no change in the absorption, excretion or serum concentration of calcium or phosphorus.

The daily administration of 100,000 units of vitamin D_2 was continued, and six weeks later balance study was reinstituted (Periods 6-12, Fig. 3). Great improvement in gastrointestinal absorption of calcium and phosphorus had occurred, for the stools now contained 60 per cent of the dietary calcium and less than 30 per cent of the ingested phosphorus. However, urinary excretion of calcium had increased to the extent that the calcium balance was barely positive (75 mg. a day). Vitamin D_2 was then increased to 500,000 units a day for eight days (periods 9 and 10), with little change in calcium or phosphorus balance. Vitamin D_2 was finally increased to 1,000,000 units daily (periods 11 and 12). The serum calcium rose to 12.8 mg., and the serum phosphorus to 2.4 mg. per 100 ml. There was little effect on calcium or phosphorus absorption, but urinary calcium excretion increased to such a degree that a negative calcium balance ensued.

FIGURE 2. *Decalcified Section of Bone Adjacent to Callus (X 450).*

For the next six weeks the patient received 100,000 units of vitamin D_2 daily, after which balance study was renewed to evaluate the effect of more prolonged vitamin D treatment. This study (periods 13 and 14) indicates that after the longer period of vitamin D_2

TABLE 1 *(Concluded).*

Blood							Gastrointestinal System				Stool	
SODIUM	POTASSIUM	CHLORIDE	CARBON DIOXIDE	UREA NITROGEN	SEROLOGIC TEST FOR SYPHILIS	ORAL GLUCOSE TOLERANCE	VITAMIN A LEVEL	VITAMIN A TOLERANCE TEST	SERUM AMYLASE	GASTROINTESTINAL SERIES	WEIGHT	FAT
milliequiv./liter	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*mg./100 ml.*			*gamma/100 ml.*	*gamma/100 ml.*	*units*		*gm./day*	%
140	4.5	100-105	21-25	13	Positive	"Normal"	75	452	84	"Normal"	100-150	1-3

*Range.
†Maximum.
‡Equivalent of 130 milliequiv./day.

there was no retention of calcium or phosphorus.

Vitamin D_2 was then continued for fifteen additional weeks, and a final balance study was conducted (periods 15-20). During the control periods calcium and phosphorus balance had not changed (periods 15-17). The phosphorus intake was then nearly doubled by the daily addition of 1 gm. of phosphorus to the diet. The serum phosphorus remained unchanged, but the serum calcium fell from 12 to 11 mg. per 100 ml. There was temporary improvement in both calcium and phosphorus balance because of increased absorption, but by the end of the study there was no significant calcium or phosphorus retention. Before vitamin D_2 therapy the serum alkaline phosphatase ranged from 5 to 8 Bodansky units; during therapy it fluctuated between 7 and 12 Bodansky units. The serum carbon dioxide remained low despite a normal blood pH and blood citric acid level.

These studies indicated the presence of two especially significant abnormalities. The first was the inability to retain absorbed calcium despite radiographic evidence of severe calcium depletion. This paradoxical rejection of calcium was further documented by repeated calcium infusions performed before and during vitamin D_2 therapy and with and without supplementary phosphorus (Table 2). Before treatment only 25 per cent of the infused load was retained. Neither vitamin D nor added phosphorus improved calcium retention.

The second important feature of this patient's disease was the apparent impairment of phosphate reabsorption. To determine the maximum capacity for phosphate reabsorption, buffered phosphate was infused (Table 3). The reabsorption capacity of 1.01 mg. per minute, which was well below normal,[14] failed to increase significantly when the serum phosphorus concentration was raised to a normal level.

Phosphorus reabsorption was also determined before, during and after a calcium infusion (Table 4). Before infusion 0.71-1.03 mg. of phosphorus was reabsorbed per minute, representing 66 to 75 per cent of the filtered load. During calcium infusion phosphorus reabsorption increased to 1.35 mg. per minute, but, since there was a slight elevation of serum phosphorus, the percentage of filtered phosphorus reabsorbed did not increase. Immediately after the infusion phosphorus reabsorption rose to 1.73 mg. per minute. Although this does not approach normal

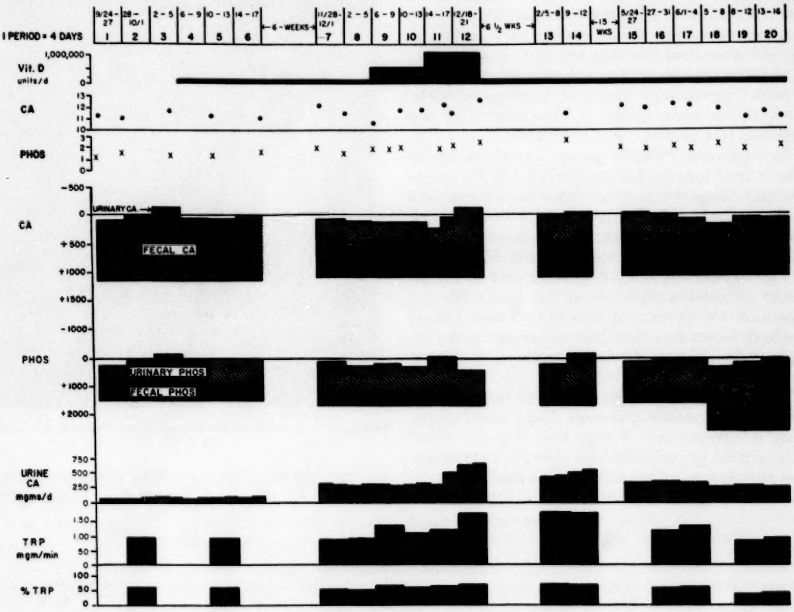

FIGURE 3. *Summary Charts of Experimental Data.*
The increase in urinary calcium and the decrease in stool calcium with vitamin D therapy are notable.

values for maximum tubular reabsorption, it represents 89 per cent of the filtered load — well within normal limits.

Phosphorus reabsorption was calculated during each balance period. Before vitamin D administration the rate was 0.97 mg. per minute, representing only 60 per cent of the filtered phosphorus (Fig. 3). During the initial administration of 100,000 units of vitamin D_2 neither the quantity nor the percentage of phosphorus reabsorbed changed. When vitamin D_2 was increased to 500,000 units daily, the amount reabsorbed rose to an average of 1.28 mg. per minute, but owing to a slight rise in serum phosphorus the percentage did not increase. During the administration of 1,000,000 units of vitamin D_2 phosphorus reabsorption rose to 1.82 mg. per minute, representing 72 per cent of the filtered load. Six weeks later similar results were obtained, although vitamin D_2 had been reduced to 100,000 units daily; the amount reabsorbed was 1.86 mg. per minute whereas the percentage remained at 72. After this dose of vitamin D_2 had been continued for fifteen additional weeks, however, the amount had dropped to an average of 1.33 mg. per minute, with a proportionate decrease in the percentage of the filtered load reabsorbed. When phosphorus was added to the diet, the amount reabsorbed fell to 0.98 mg. per minute, approaching the values obtained before the institution of vitamin D_2 therapy, and the percentage decreased markedly. Only 43 per cent of the inorganic phosphorus filtered through the glomerular membrane was reabsorbed by the renal tubular cells.

TABLE 2. *Calcium Infusion Tests.*

DATE	THERAPY	CALCIUM RETAINED
		%
July 17, 1954	None	25.0
Nov. 16, 1954	100,000 units of vitamin D/day	22.3
May 17, 1955	100,000 units of vitamin D/day for 8 mo.	6.9
June 17, 1955	100,000 units of vitamin D/day for 9 mo. & 1 gm. of supplementary phosphorus	24.1

DISCUSSION

We are unable to fit this case into a recognized clinical syndrome, nor are we able to explain the etiology of the osteomalacia.

There are similarities to the cases described by Albright and Reifenstein,[1]* McCance,[7] and Kyle et al.,[15] which are characterized by low serum phosphorus, pseudofractures, elevated fecal calcium and low tubular reabsorption of phosphate.

Although our initial impression was that the patient had some form of renal disease, extensive renal-function tests were negative. When given 150 milliequiv. of ammonium chloride a day, he was able to accommodate to this fixed anion load by increasing his urinary ammonia and titratable acid production in a manner comparable to that of normal controls.[16] The absence of hypercalciuria was further evidence against renal disease as the explanation of the osteomalacia. Even though renal disease was considered unlikely the blood carbon dioxide remained mildly depressed.

*In their Case 21 (p. 211), more striking benefit was obtained through the use of vitamin D therapy, however, than in the case reported here.

TABLE 3. *Maximum Reabsorptive Capacity for Phosphorus.*

PERIOD	SERUM PHOSPHORUS	AMOUNT OF PHOSPHORUS FILTERED	AMOUNT OF PHOSPHORUS EXCRETED	PHOSPHORUS REABSORBED	
				AMOUNT	PERCENTAGE
	mg./100 ml.	*mg./min.*	*mg./min.*	*mg./min.*	
0	1.3	1.62	0.61	1.01	62
1	2.2	2.75	1.57	1.18	43
2	3.5	4.37	3.25	1.12	26
3	3.6	4.50	3.66	0.84	19

Attention was then given to the gastrointestinal tract. The vitamin A blood level, the prothrombin time and the absorption of orally administered vitamin A were normal, indicating adequate absorption of fat-soluble vitamins. Stool analyses showed normal amounts of fat; thus, the diagnosis of vitamin deficiency secondary to poor fat absorption was not tenable.

At this point it was found that there was no change in the calcium absorption after twelve days of vitamin D_2 administration (100,000 units a day). After six weeks of such therapy, however, calcium absorption was greatly improved. Larger amounts of vitamin D_2 caused no significant increase in calcium and phosphorus absorption, but striking hypercalciuria ensued. Consequently, the patient was maintained on 100,000 units of vitamin D_2 daily. Although vitamin D_2 improved calcium absorption, it failed to produce positive calcium balance necessary for healing the osteomalacia. Thus, faulty absorption is not the sole defect producing the skeletal disease.

Inability to retain either absorbed or infused calcium was a striking abnormality in this patient. In a series of normal subjects, approximately 55 per cent of calcium given intravenously was retained.[11] Much greater calcium retention has been noted in patients with osteomalacia.[10] This patient retained only 25 per cent of the infused calcium. Neither prolonged vitamin D therapy nor additional dietary phosphorus corrected this defect. The data obtained during acute loading experiments, as well as from balance study, indicate that this patient fails to benefit from either vitamin D therapy or the infusion of calcium.

An additional abnormality exhibited by this patient is excessive phosphorus excretion. Dent[17] believes

that impaired reabsorption of phosphorus is the primary defect in some patients with osteomalacia. This tubular defect causes inadequate reabsorption of filtered phosphorus, producing hypophosphatemia. There may or may not be associated tubular defects resulting in glycosuria, amino-aciduria, hyperkaluria, hyposthenuria or inability to synthesize ammonia ions or produce an acid urine. Furthermore, Dent maintains that very large amounts of vitamin D will improve or correct the defect in tubular function that the serum calcium. Some of the data obtained in this study lend support to this concept. During and after the calcium infusion both the amount and the percentage of phosphorus reabsorbed increased. This could be attributed to diminished production of parathyroid hormone caused by the elevation of serum calcium.[12] Thus released from parathyroid stimulation, the renal tubule can reabsorb more phosphorus. Such an interpretation could be employed again in the explanation of the increase in the amount and percentage reab-

TABLE 4. *Phosphorus Reabsorption before, during and after Calcium Infusion.*

TIME	SERUM PHOSPHORUS	CREATININE CLEARANCE	PHOSPHORUS CLEARANCE	AMOUNT OF PHOSPHORUS FILTERED	AMOUNT OF PHOSPHORUS EXCRETED	PHOSPHORUS REABSORBED		RATIO OF PHOSPHORUS-TO-CREATININE CLEARANCE
						AMOUNT	PERCENTAGE	
hr.	*mg./100 ml.*	*ml./min.*	*ml./min.*	*mg./min.*	*mg./min.*	*mg./min.*		
Before infusion:								
−26 to −2	0.96	123	41	1.18	0.40	0.78	66	0.34
−2 to −1	1.13	86	23	0.97	0.26	0.71	74	0.26
−1 to 0	1.10	125	31	1.37	0.34	1.03	75	0.25
During infusion:								
0 - 1	1.15	132	41	1.52	0.47	1.05	69	0.31
1 - 2	1.26	139	49	1.75	0.61	1.14	65	0.35
2 - 3	1.45	131	38	1.90	0.55	1.35	71	0.29
After infusion:								
3 - 4	1.28	132	22	1.69	0.28	1.41	83	0.17
4 - 5	1.14	105	14	1.20	0.15	1.05	87	0.13
5 - 24	1.56	125	14	1.95	0.22	1.73	89	0.11
24 - 48	1.21	115	27	1.39	0.33	1.06	76	0.24

leads to the excessive loss of phosphorus. Other investigators as well[12,18-20] have found that vitamin D increases the fraction of filtered phosphorus reabsorbed by the normal kidney in man and dogs.

The ability of this patient to reabsorb filtered phosphorus has been studied periodically, and during massive vitamin D_2 therapy both the amount and the percentage reabsorbed increased appreciably. Although this could be used as evidence in support of Dent's thesis, the increases that immediately followed calcium infusion and the decrease in phosphorus reabsorption during increased phosphorus intake are difficult to explain by a tubular defect. Another line of reasoning to explain the persistently defective phosphorus reabsorption displayed by this patient could be advanced — namely, that he has osteomalacia with secondary hyperparathyroidism. Albright and Reifenstein[1] have provided data indicating that rickets that is due either to defective calcium absorption or to excessive calciuria is associated with hyperphosphaturia. This they attribute to secondary hyperparathyroidism. Initial hypocalcemia presumably stimulates parathyroid activity, with a consequent increase in urinary phosphorus excretion, hypophosphatemia and rise in sorbed observed during the administration of 1,000,000 units of vitamin D, for improvement in phosphorus reabsorption was associated with abnormally high concentrations of serum calcium. During supplementary phosphorus, although the serum phosphorus did not rise to normal values, it did remain consistently higher than this patient's base-line concentration. We might reason that this "relative" hyperphosphatemia caused a still greater stimulation of the parathyroid gland to produce additional hormone. Consequently, further inhibition of phosphorus reabsorption occurred, and both amount and percentage fell. After these observations of the turning on and off of parathormone activity calcium absorption was adequate during the eight-month period of vitamin D_2 therapy, without evident improvement in either calcium retention or phosphorus reabsorption. If hypocalcemia was the initial stimulus to secondary hyperparathyroidism it is difficult to understand the persistence of hyperparathyroidism after the restoration of calcium to normal levels. In the examples of secondary hyperparathyroidism presented by Albright and Reifenstein,[1] however, this paradox exists.

There are four theoretical causes of osteomalacia:

decreased intestinal absorption of calcium; increased urinary calcium excretion; excessive urinary phosphorus loss; and impairment of gastrointestinal absorption of phosphorus. Before treatment, intestinal calcium absorption and renal phosphorus reabsorption were strikingly abnormal. During vitamin D therapy increased calcium excretion in the urine became the dominant defect. Both the original abnormalities were amenable to temporary improvement, but there was no evidence of skeletal remineralization. Consequently, it is impossible to blame a single metabolic abnormality in an explanation of the total picture. The theory that the primary defect is in absorption of calcium, with the complication of secondary hyperparathyroidism, does not fit all the facts. Nor does the supposition that the primary abnormality is in the renal tubule explain all the abnormalities observed in this patient. One might suggest that the defect is in the bone itself — that because of some unknown disturbance, such as the deficiency of an essential enzyme or transport system or an unrecognized abnormality in the protein matrix, normal mineralization of the osteoid could not occur. This does not explain either the defective absorption of calcium or the reabsorption of phosphorus.

Summary

A twenty-five-year-old Negro with chemical and radiologic evidence of osteomalacia was studied by both balance and infusion technics. The most striking defects in mineral metabolism were as follows: defective absorption of calcium from the gastrointestinal tract — correctable by vitamin D_2 therapy; a marked increase in the clearance of phosphorus — temporarily reduced to normal by the stimulus of hypercalcemia; and inability to retain either absorbed or infused calcium. Neither "raised resistance to vitamin D" nor primary renal phosphaturia offer an adequate explanation for this picture.

After this manuscript had been completed, Dr. C. E. Dent kindly let us see a portion of a report in preparation describing 4 cases, strikingly similar to our own. The features of these were low serum phosphorus, normal serum calcium, low serum carbon dioxide and normal tubular function. Thus, these 4 cases, as well as the case presented above, may represent a newly recognized type of bone disease.

We are indebted to Lieutenant Elaine Shipman, WMSC, and to Captain Florence Berger, WMSC, for the preparation of the diets, to Captain Johnnie Long, ANC, and her nursing staff, and especially to the patient, without whose enthusiastic co-operation this study would not have been possible. Major William H. Meroney was helpful in the over-all plan of these studies, and Miss Marjorie Knowlton supervised all determinations. Mrs. Doris Blackmon rendered extensive secretarial assistance.

References

1. Albright, E., and Reifenstein, E. C., Jr. *The Parathyroid Glands and Metabolic Bone Diseases: Selected studies.* 393 pp. Baltimore: Williams & Wilkins, 1948.
2. Looser, E. Über Spätrachitis und Osteomalacie: klinische, röntgenologische und pathologisch-anatomische Untersuchungen. *Deutsche Ztschr. f. Chir.* **152**:210-357, 1920.
3. Albright, F., and Sulkowitch, H. W. Effect of vitamin D on calcium and phosphorus metabolism: studies on four patients. *J. Clin. Investigation* **17**:305-315, 1938.
4. Albright, F., Butler, A. M., and Bloomberg, E. Rickets resistant to vitamin D therapy. *Am. J. Dis. Child.* **54**:529-547, 1937.
5. Albright, F., Burnett, C. H., Parsons, W., Reifenstein, E. C., Jr., and Roos, A. Osteomalacia and late rickets: various etiologies met in United States with emphasis on that resulting from specific form of renal acidosis, therapeutic indications for each etiological sub-group, and relationship between osteomalacia and Milkman's syndrome. *Medicine* **25**:399-479, 1946.
6. McCune, D. J., Mason, H. H., and Clarke, H. T. Intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome): report of case in which increased urinary organic acids were detected and identified, with review of literature. *Am. J. Dis. Child* **65**:81-146, 1943.
7. McCance, R. A. Osteomalacia with Looser's nodes (Milkman's syndrome) due to raised resistance to vitamin D. *Quart. J. Med.* **16**:33-46, 1947.
8. Knowlton, M., Ed. *Analytical Methods.* 198 pp. (Published by Army Medical Service Graduate School, Walter Reed Army Medical Center.) Washington, D. C.: Government Printing Office, 1955.
9. Howard, J. E., Hopkins, T. R., and Connor, T. B. On certain physiologic responses to intravenous injection of calcium salts into normal, hyperparathyroid and hypoparathyroid persons. *J. Clin. Endocrinol.* **13**:1-19, 1953.
10. Kyle, L. H., Schaaf, M., and Erdman, L. A. Metabolic effects of intravenous administration of calcium. *J. Lab. & Clin. Med.* **43**:123-133, 1954.
11. Meyer, R. J., Kyle, L. H., and Schaaf, M. Calcium retention following intravenous calcium in osteoporosis. *Clin. Research Proc.* **3**:76, 1955.
12. Nordin, B. E. C., and Fraser, R. Effect of intravenous calcium on phosphate excretion. *Clin. Sc.* **13**:477-490, 1954.
13. Schaaf, M., and Kyle, L. H. Measurement of per cent renal phosphorus reabsorption in diagnosis of hyperparathyroidism. *Am. J. M. Sc.* **228**:262-268, 1954.
14. Klein, R., and Gow, R. C. Interaction of parathyroid hormone and vitamin D on renal excretion of phosphate. *J. Clin. Endocrinol.* **13**:271-282, 1953.
15. Kyle, L. H., Meroney, W. H., and Freeman, M. E. Study of mechanism of bone disease in hypophosphatemic glycosuric osteomalacia. *J. Clin. Endocrinol.* **14**:365-377, 1954.
16. Segar, W. E., and Fremont-Smith, K. Unpublished data.
17. Dent, C. E. Rickets and osteomalacia from renal tubule defects. *J. Bone & Joint Surg.* **34B**:266-274, 1952.
18. Pitts, R. F., and Alexander, R. S. Renal reabsorptive mechanism for inorganic phosphate in normal and acidotic dogs. *Am. J. Physiol.* **142**:648-662, 1944.
19. Freeman, S., and Dunsky, I. Resistant rickets. *Am. J. Dis. Child.* **79**:409-427, 1950.
20. Harrison, H. E., and Harrison, H. C. Renal excretion of inorganic phosphate in relation to action of vitamin D and parathyroid hormone. *J. Clin. Investigation* **20**:47-55, 1941.

OUTCOME OF SOLITARY PULMONARY NODULES DISCOVERED IN AN X-RAY SCREENING PROGRAM*

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SOLITARY pulmonary nodules have caused considerable concern ever since the advent of roentgenography made their detection possible during life. This concern has been heightened in recent years by the high proportion of malignant neoplasms found in many series of excised nodules.[1-4] This finding, together with the low mortality and morbidity associated with modern chest surgery, has led clinicians to consider removal of a solitary nodule almost immediately upon discovery. Although such a practice seems sound in the light of present limited knowledge, the management of these solitary nodules would be on much firmer ground if the risks for those not surgically excised could be delineated as clearly as they are for those that are now being resected. Except for a recent report by Hillerdal,[5] all reported series of pulmonary nodules with which we are familiar are limited to resected cases, or to those that produced disability or death.

The purpose of the present report is to record our experience with solitary pulmonary nodules detected in an extensive x-ray screening program in Muscogee County, Georgia. This series, although selected by the factors that induce people to accept x-ray examination of the chest, is thought to be a more representative sample of solitary pulmonary nodules than those included in previously published reports.

SELECTION OF CASES

Cases for the study were drawn from the records of the Muscogee County Tuberculosis Study, a cooperative facility supported by the Georgia Department of Public Health, Muscogee County Health Department and the United States Public Health Service.[6,7] Between May 1, 1946, and January 1, 1954, approximately 300,000 x-ray examinations of the chest were made in the tuberculosis case-finding program — about half of them in mass surveys and the remainder in the Health Department Chest Clinic. Films were taken in the Chest Clinic for a wide variety of reasons, ranging from routine preemployment examinations to investigations of persons with pulmonary symptoms. Nearly all the population studied resided in the study area (Muscogee and Harris counties, Georgia, and Russell County, Alabama, which together had a 1950 census population of 169,657).

A preliminary selection of prospective cases for the study was made from records of persons who had had at least one 14-x-17 film between May 1, 1946, and January 1, 1954. All persons with a diagnosis of pulmonary neoplasm of any type or pulmonary mass or calcification were considered prospective cases, as were those classified as having pulmonary tuberculosis or suspected tuberculosis in whose x-ray descriptions any of the following terms appeared: nodule, nodular mass, tumor, granuloma, tuberculoma, histoplasmoma, halo calcification, coin lesion or nummular shadow. It is believed that no persons with pulmonary nodules were overlooked in the preliminary selection.

To restrict the group of prospective cases to persons with solitary pulmonary nodules, the initial chest x-ray films¶ were reviewed by one of us (R.H.V.) who had no previous knowledge of any of the cases. He was not given access to clinic records or subsequent films until he had decided whether or not the prospective cases met the following criteria, the first four of which were taken from a paper by Good, Hood and McDonald[8]:

The mass appeared to be within the substance of the lung.

It was the only x-ray evidence of significant pulmonary disease.

There was no x-ray evidence of bronchial obstruction.

There was no x-ray evidence of cavitation (no planigrams were available).

Masses that appeared to be completely or largely (over 50 per cent) calcified were excluded.

The size or shape of the mass was not a selective factor.

The border of the density was sufficiently discrete to justify the term "mass" rather than "infiltrate," but except for this the sharpness of the border was not a selective factor.

From the review of several thousand clinic records, and the examination of several hundred films, 88 persons were selected whose initial x-ray findings met the criteria listed above. It is believed that the selection tended to be very strict, so that persons with even suggestive evidence of associated pulmonary disease or more than a slight amount of calcification were excluded.

*Presented in part at the annual meeting of the Medical Association of Georgia, May 3, 1955.

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¶"Initial film" was defined as the first 14-x-17 chest film in which the pulmonary nodule was noted. It always included a posteroanterior view and often lateral or other views of the chest.

Follow-up Study

The routine follow-up procedures varied according to the initial film reader's impression of the presence or absence of calcification. Those with calcification in the nodule were merely advised to have chest x-ray examinations repeated annually; those without calcification were advised to be examined every three months for several years, and after 1949, to consult their own physicians regarding the advisability of excision. We have the impression that persons with symptoms referable to the chest followed this advice more closely than those without symptoms. In 1954 an intensive effort was made to locate each of the 88 persons. Those still living in or near the study area were requested to return for another 14-x-17 chest film, tuberculin and histoplasmin tests and sputum examinations for acid-fast bacilli. Skin tests were not repeated, however, when previous tests had been strongly positive. The patients who had moved from the area were sent questionnaires. A letter was sent to the physicians of those who could be located, to ascertain the current status of their health.

It was possible to make a reasonably definite diagnosis of the cause of the pulmonary nodule in 11 of the 88 cases. Four patients were considered to have carcinoma of the lung. In 3 cases, the diagnosis was based on pathological examination of the resected lesion—2 of these were bronchogenic carcinoma, and the other adenocarcinoma. The diagnosis in the fourth case was based on clinical and x-ray evidence, since the patient's poor general condition and age (seventy-five years) made thoracotomy seem unduly hazardous. The subsequent course was typical of bronchogenic carcinoma, and, although not proved, the diagnosis seems reasonable.

In 4 cases pulmonary tuberculosis was diagnosed by the finding of acid-fast bacilli in the sputum. Three patients were hospitalized for varying periods. One of these patients had the nodule resected, but died of a subsequent contralateral spread. A fifth patient had only a single examination at our clinic, evaded follow-up study by moving to another state and later died. We were unable to obtain a report of sputum examination, but an x-ray film taken shortly before death showed bilateral cavitary disease, and it seems reasonable to accept the death-certificate diagnosis of pulmonary tuberculosis.

Two other persons had their nodules excised. The nodule in 1 was a granuloma with some histologic features suggesting a foreign-body reaction, and occurred in a known alcoholic patient. The other was a granuloma with no histologic features suggesting the etiology — tuberculin and histoplasmin tests were both negative. The diagnosis in the remaining 77 cases is still undetermined.

The follow-up status of the group on March 5, 1955, is shown in Table 1. All the 57 persons living in our area were approached personally, and, although 14 of them had not been examined within the past year, all were alive and apparently well. Of 14 known to be residing elsewhere, 7 returned for examination and were well; of the other 7 (who replied by mail) 6 reported that they were in good health, and the seventh did not mention his health status. The status of 7 persons on March 5, 1955, was completely unknown. However, 2 of them had been followed in the clinic for seventy-nine and twenty-one months, respectively, and were alive and well at the last examination. One of the 7 had only one examination, but was known to be alive and apparently well twelve months later. The remaining 4, all apparently short-term residents of the area, had only a single examination and could not be traced. Ten persons are known to have died.

Table 1. *Follow-up Status of 88 Patients with Nodules on March 5, 1955.*

Status		No. of Patients
Living in study area		57
Examined in past year	43	
Apparently well; no recent examination.	14	
Living elsewhere		14
Examined in past year	7	
Apparently well; no recent examination.	6	
Health unknown; no recent examination.	1	
Unknown		7
Dead		10
Causes related to nodule	5	
Other causes	5	

For the entire series, the median period of observation from first to last clinic examination was forty-nine months. Fourteen persons had only an initial examination, and 22 had been observed for five years or more. The median interval from date of first clinic examination to the date of latest information was fifty-three months.

Of the 10 deaths known to have occurred in the total group of 88 persons, 5 were from causes directly associated with the pulmonary nodule. Three of these were from carcinoma of the lung: 1 was considered inoperable at the time of detection because of the general condition of the patient; another patient died after a palliative resection after refusing surgery when the nodule was first detected; and the third died from a postoperative coronary occlusion after successful pulmonary resection. Two patients died from pulmonary tuberculosis. The other 5 deaths were from causes apparently unrelated to the pulmonary nodule — 3 from coronary-artery disease, 1 from congestive heart failure, and 1 from nephritis. The median interval from first clinic examination to death was twenty-seven months. No deaths have occurred among those observed for more than fifty-six months.

Source of Referral

Although this series of 88 solitary pulmonary nodules cannot be considered unselected, it may be fairly representative of persons with nodules in the study area because of the large number and variety of x-ray examinations from which they were drawn. The great majority (91 per cent) of the patients detected by mass survey had no symptoms referable to the lesion. Somewhat more nodules were found among males, in spite of the fact that the screened population contained slightly more females than males. The low proportion of solitary nodular lesions in Negroes is particularly striking, since Negroes comprised about two-fifths of the total population surveyed. All of the carcinomas occurred in white men, the youngest being thirty-four and the oldest seventy-five years of age. Two cases of tuberculosis occurred among white females, two among Negro males, and one in a Negro female.

Table 2. *Source of Referral According to Final Diagnosis.*

Final Diagnosis	Patient Suspected of Having Tuberculosis	Contacts of Patients with Tuberculosis	Patients Referred by Private Physicians	Patients Self-Referred	Patients Examined in Mass Survey	Food Handlers	Other "Routine" Referrals	Totals
Cancer					3	1		4
Tuberculosis		1	2		2			5
Granuloma			1		1			2
Undetermined	1	1	8	11	35	11	10	77
Totals	1	2	11	11	41	12	10	88

nied symptoms. This may bear some relation to the fact that such a low proportion of the series has been demonstrated to have carcinoma, for others have found that "patients with primary malignant disease were most likely to complain of symptoms."[3] The type of referral for each of the diagnostic groups is shown in Table 2.

Table 3. *Prevalence of Nodules in 1946 Surveys According to Race and Broad Age Groups.*

Age at Time of Survey	White Persons			Negroes		
	Population Surveyed	No. of Cases	Rates per 1000	Population Surveyed	No. of Cases	Rates per 1000
yr.						
25-44	14,028	13	0.9	10,167	3	0.3
>45	6,336	10	1.6	3,971	5	1.3
Totals	20,364	23		14,138	8	
Averages >25			1.1			0.6

The mass survey of 1946 affords some idea of the prevalence of solitary pulmonary nodules (Table 3). In that program, 34,502 persons over the age of 25 were examined, and among them 31 such nodules were found. This is equivalent to a prevalence ratio of 0.9 per 1,000. The prevalence increased with age, and was greater among whites than among Negroes.

Clinical Features

The age, race and sex distribution of the group is shown in Table 4. More than half the persons were forty years of age or older. Although exact figures are not available for the entire group of those given x-ray examination from which the nodule group is drawn, it is believed that about a third were over forty. Only 1 nodule, later shown to be tuberculous, was found in a person less than twenty years of age.

Tuberculin tests, using 0.0001 mg. of P.P.D., were given to 79 of the 88 persons with nodules; 65 of them also had histoplasmin tests. The results are shown in Table 5. The definition of a positive reaction was the observation, forty-eight to seventy-two hours after testing, of an area of induration 5 mm. or more in diameter. Of those tested, 61 per cent were positive reactors to tuberculin, which is not significantly different from the expected rate of positive reactors for a group of this age, race and sex composition.[9] Two thirds of those tested had a positive reaction to histoplasmin. Although comparable data are not available for the general population, the study area is not in the area of high histoplasmin sensitivity, and the proportion of positive reactors in the present study group was much higher than that in any other group tested in our clinic, with the exception of persons with disseminated pulmonary calcifications. This suggests that many of the nodules may have been due to histoplasmosis.

Table 4. *Distribution of Nodule Group According to Age at First Examination and Sex.*

Age at First Examination	White Persons			Negroes	
	Totals	Males	Females	Males	Females
yr.					
0-19	1			1	
20-39	36	19	13	2	2
40-59	41	18	16	3	4
60 & over	10	3	4	3	
Totals	88	40	33	9	6

The initial size of the pulmonary nodule is shown in Table 6. Somewhat more than half were larger than

12 mm. in diameter, and only 9 were 28 or more mm. in diameter. However, among these 9 were concentrated the more serious lesions, 3 of them being carcinoma, and another 3 tuberculosis. One of the smaller tuberculous nodules was associated with positive sputum on only one occasion — the patient remained well with no treatment other than mild restriction of activity. The association of size of nodule with seriousness of disease has been noted by other authors.[4,8,10]

TABLE 5. *Tuberculin and Histoplasmin Sensitivity of Group with Nodules.*

TUBERCULIN SENSITIVITY		HISTOPLASMIN SENSITIVITY		
	TOTALS	POSITIVE TESTS	NEGATIVE TESTS	PERSONS NOT TESTED
Positive	48	19	18	11
Negative	31	24	4	3
Not tested	9			9
Totals	88	43	22	23

A number of studies[8,10] have suggested that the x-ray appearance of calcification or lamination within the nodule is of considerable help in ruling out the presence of cancer. Consequently, the initial x-ray films of the chest in our series were inspected carefully for such evidence. It should be recalled in this connection that nodules appearing to be more than 50 per cent calcified were excluded from the series, and

TABLE 6. *Size of Nodule on Initial Posteroanterior Chest Film According to Diagnosis.*

DIAMETER	NO. OF CASES	FINAL DIAGNOSIS		
		CASES OF CANCER	CASES OF TUBERCULOSIS	CASES OF GRANULOMA
mm.				
5-7	5			
8-12	35		1	1
13-17	21		1	
18-22	12	1		
23-27	6			1
28-32	5	1	2	
33-37	2	1		
37 & over	2	1	1	
Totals	88	4	5	2

also that planigraphy was not done; 26 of the nodules showed definite or questionable calcification, and 17 definite or questionable lamination (Table 7). Ten patients had some evidence of both calcification and lamination; 55 of the 88 had neither. Tuberculin and histoplasmin tests were done on 22 of the persons with calcification and on 14 of those with lamination. Of the 22 with calcification, 13 (59 per cent) were positive reactors to tuberculin, and 15 (68 per cent) to histoplasmin, whereas among the 14 with lamination, 7 (50 per cent) were positive to tuberculin, and 12 (86 per cent) to histoplasmin. Several of the laminated nodules had the central dot of calcification described as being characteristically associated with histoplasmin sensitivity.[11]

TABLE 7. *Evidence of Calcification or Lamination in Initial Film.*

CALCIFICATION		CASES OF LAMINATION		
	TOTALS	DEFINITE	QUESTIONABLE	NONE
Definite	14	3		11
Questionable	12	3	4	5
None	62	4	3	55
Totals	88	10	7	71

None of the 33 persons with suggestive evidence of calcification or lamination had any symptoms or disability attributable to the nodule, nor did they give any evidence of active tuberculosis or carcinoma. One lesion was resected and found to be a granuloma.

Some evidence of change in the x-ray appearance of the nodule was noted in 35 of the 88 cases (Table 8). An increase in size was noted in 10. Two of these were later shown to be carcinomas, and 2 to be tu-

TABLE 8. *Changes Observed in the X-Ray Appearance of Nodules in Follow-up Period.*

No change		36
Increased calcification only		9
Increase in size only		10
Decrease in size		16
Decrease in size only	8	
Disappearance of nodule	2	
Decrease in size, with increase in calcification	6	
Lesion resected; no previous change.		3
No film for comparison		14
Total		88

berculosis. All 4 of these persons died; only 1 with carcinoma and 1 with tuberculosis refused treatment until the disease was advanced, another with tuberculosis suffered a contralateral spread postoperatively in the preantibiotic era, and the other with carcinoma was too poor a risk for thoracotomy. Although the other 6 whose lesions showed some increase in size are still alive and well, the concentration of 4 fatal cases in this small subgroup suggests the serious potentiality of a lesion that enlarges under observation. It is of interest that 2 nodules, each of fair size originally (22 and 10 mm.), were observed to disappear completely, leaving no x-ray evidence of their previous existence. A third nodule (14 mm.) also disappeared abruptly, leaving only a small fibrotic scar. These patients had no significant symptoms and have remained well, without other evidence of pulmonary disease, for several years since the disappearance of

the nodule; no x-ray changes had been noted before the nodules disappeared. It is assumed that the lesions excavated and that their contents were expectorated without producing bronchogenic spread. Other authors[12,13] have emphasized the fact that round foci due to tuberculosis are often benign in their subsequent course, even when excavation occurs.

TABLE 9. *Expected and Observed Deaths among the Nodule Group.*

GROUP	DEATHS	
	EXPECTED	OBSERVED
Total nodule group	5	10
Nodules without calcification or lamination	3	10

Sputum was submitted for examination by only 12 patients. Of these the sputum of 4 was positive for acid-fast bacilli culturally similar to tubercle bacilli. Of the 4, 3 required treatment at some time during the illness. One had a single positive sputum but has remained well, with no subsequent evidence of active disease that could be revealed by careful long-term observation.

PROGNOSIS

It is not possible from such a small series to predict accurately the number of deaths that might have been expected. However, an estimate was made according to the method suggested by Sartwell,[14] utilizing the 1950 mortality experience of the state of Georgia, with adjustment for age only. The results of the calculations are shown in Table 9, both for the entire group of 88 persons and for the 55 without any suggestion of calcification or lamination within the nodule. It should be noted that the 5 deaths observed from causes apparently unrelated to the pulmonary nodules corresponded to the number of expected deaths. These results suggest that the risk of dying is appreciably greater among persons with solitary pulmonary nodules than it is for the general population of the same age, and that the increased risk can be attributed to carcinoma of the lung and pulmonary tuberculosis.

Consequently, one is not justified in recommending a regimen of watchful waiting for *all* persons with solitary pulmonary nodules. On the other hand, since only 4 out of the 88 persons in the series have been shown to have had carcinomas, one can hardly advise indiscriminate excision. It appears essential that cases be selected for surgical treatment by the careful application of the diagnostic leads already known, and that the search be continued for more adequate diagnostic clues to the nature of these nodules.

SUMMARY AND CONCLUSIONS

A series of 88 persons with solitary pulmonary nodules was found in the records of the Muscogee County Tuberculosis Study. The median period of observation was fifty-three months.

Solitary pulmonary nodules were observed more frequently among males than females, among whites than Negroes, and among those over forty than among those under this age. They were associated with histoplasmin sensitivity, but not with tuberculin sensitivity.

Only 4 carcinomas were diagnosed, all among white males. Five nodules were demonstrated to be tuberculous, and 2 were granulomas of undetermined etiology.

Size of the nodules appeared to be an important diagnostic clue. Among 9 nodules with a diameter greater than 28 mm., 3 were carcinomas, and 3 tuberculosis. Presence of calcification or lamination also appeared useful: no carcinoma or tuberculosis was demonstrated among those with either of these features.

Ten of the 88 persons are known to have died, 5 from causes apparently related to the pulmonary nodule. Three of these deaths were due to carcinoma, and 2 to tuberculosis. The observed number of deaths was two or three times the expected number, and the excess appeared to be due to carcinoma and tuberculosis.

It is suggested that neither routine observation nor indiscriminate excision can be recommended, and that further knowledge regarding the fate of these lesions — those excised as well as those not excised — would help delineate the risks involved in various methods of treatment. With such information, the management of persons with solitary pulmonary nodules could be placed on a more rational basis than is now possible.

REFERENCES

1. Effler, D. B., Blades, B., and Marks, E. Problem of solitary lung tumors. *Surgery* **24**:917-928, 1948.
2. Jones, R. C., and Cleve, E. A. Solitary, circumscribed lesions of lung; selection of cases for diagnostic thoracotomy. *Arch. Int. Med.* **93**:842-849, 1954.
3. Hood, R. T., Jr., Good, C. A., Clagett, O. T., and McDonald, J. R. Solitary circumscribed lesions of lung; study of 156 cases in which resection was performed. *J.A.M.A.* **152**:1185-1191, 1953.
4. Wilkins, E. W., Jr. Asymptomatic isolated pulmonary nodule. *New Eng. J. Med.* **252**:515-520, 1955.
5. Hillerdal, O. Tuberculoma of lung. *Acta tuberc. Scandinav.* Supp. 34:1-91, 1954.
6. Comstock, G. W. Tuberculosis studies in Muscogee County, Georgia. 1. Community-wide tuberculosis research: x-ray findings in community-wide survey and its coverage as population census. *Pub. Health Rep.* **64**:259-290, 1949.
7. Comstock, G. W., and Sartwell, P. E. Tuberculosis studies in Muscogee County, Georgia. IV. Evaluation of community-wide x-ray survey on basis of six years of observation. *Am. J. Hyg.* **61**: 261-285, 1955.
8. Good, C. A., Hood, R. T., Jr., and McDonald, J. R. Significance of solitary mass in lung. *Am. J. Roentgenol.* **70**:543-554, 1953.
9. Comstock, G. W. Place of tuberculin testing in tuberculosis control program. 1. Tuberculin testing in relation to case finding. *Tr. Nat. Tuberc. A.* **48**:726-736, 1952.
10. Rigler, L., and Heitzman, E. R. Planigraphy in differential diagnosis of pulmonary nodule: with particular reference to notch sign of malignancy. *Radiology* **65**:692-702, 1955.
11. Furcolow, M. L., Mantz, H. L., and Lewis, I. Roentgenographic appearance of persistent pulmonary infiltrates associated with sensitivity to histoplasmin. *Pub. Health Rep.* **62**:1711-1718, 1947.
12. Campbell, A. H. Spontaneous disappearance of tuberculomata of lung. *M. J. Australia* **2**:242-245, 1955.
13. Macleod, W. M., and Smith, A. T. Some observations on historical appreciation, pathological development, and behaviour of round tuberculous foci. *Thorax* **7**:334-355, 1952.
14. Sartwell, P. E. Time factor in studies of outcome of chronic disease. *Am. Rev. Tuberc.* **63**:608-612, 1951.

RENAL FUNCTION AFTER RECOVERY FROM ACUTE RENAL FAILURE*

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BOSTON

A NUMBER of investigators have studied the recovery of renal function after acute renal failure.[1-10] The clearance of inulin, thiosulfate, mannitol, creatinine, para-aminohippurate and iodopyracet (Diodrast) have been found to be low early in the diuretic phase during recovery. After this, the clearance of these substances increases and returns toward the normal state.

Lowe[5] has reported a long-term follow-up study of 14 cases of acute renal failure. In his series, clinical recovery was good, but clearance values remained below the lower limit of normal for as long as three years.

This paper records another long-term follow-up study of 16 patients who recovered from acute renal failure.

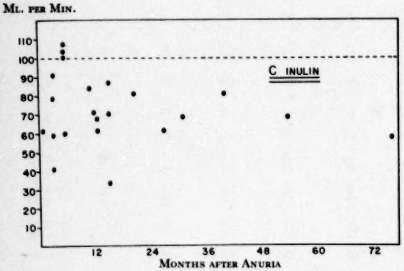

FIGURE 1. *Values for Inulin Clearance at Varying Intervals after the Onset of Acute Renal Failure. The dotted line indicates approximately normal values for this laboratory. The range is approximately 125±25 ml. per minute per 1.73 square meters of body-surface area.*

MATERIAL

Sixteen patients who had recovered from acute renal failure were selected. These subjects were picked from a large series because of the absence of any cardiovascular or renal disease before the acute episode. The patients were studied when available; in 10, more than one observation was possible.

METHODS

Each patient was admitted to the Peter Bent Brigham Hospital for twenty-four hours. Water was withheld from 6 p.m. to 6 a.m., and the specific gravity of the urine was subsequently determined; a value of 10.24 obtained under these conditions was assumed to be "normal," although it is recognized that single determinations in normal persons occasionally fall below this limit.

Clearance studies were done in the fasting state. Constant infusion rates of inulin and para-aminohippuric acid solutions were maintained by means of an infusion pump. The bladder was catheterized. Clearance values were the average of four or more periods. After the clearance studies, a fifteen-minute phenolsulfonphthalein test was performed.

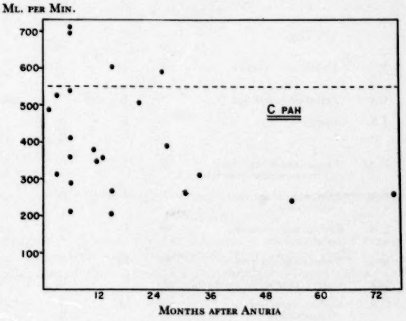

FIGURE 2. *Values for the Clearance of Para-aminohippurate at Varying Intervals after the Onset of Acute Renal Failure. The dotted line indicates approximately normal values for this laboratory. The range is approximately 650±100 ml. per minute per 1.73 square meters of body-surface area.*

Inulin determinations on serum and urine were done by Schreiner's[11] modifications of Roe's method. Para-aminohippuric acid determinations were performed by the method of Smith et al.[12] The urea concentrations in both blood and urine were determined by the method of Archibald.[13]

Clearance values for inulin and para-aminohippuric acid were corrected to 1.73 square meters of body-surface area.

RESULTS

All the patients studied made excellent clinical recovery from acute illness and have since enjoyed good health with 1 exception (subject J. B.), in whom periarteritis nodosa subsequently developed, which may explain the successive decrease in her clearance values.

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The pertinent data are summarized in Table 1. Four graphs (Fig. 1-4) show how the results of clearances compare with the expected "normal" values obtained in this laboratory. It has been assumed that these patients had "normal" renal function before the episodes of acute renal failure.

Clearance values obtained for the majority of the patients fell below the lower limit of normal. Patients studied more than once show successive increase in clearances with the one exception mentioned above. Good recovery of renal function is obtained within six months and sustained beyond that period provided other diseases do not intervene. There is no relation between the severity and duration of acute renal failure and the degree of residual function.

It should be noted that the specific gravity and phenolsulfonphthalein excretion were usually within normal limits when clearance studies indicated that renal function was subnormal.

TABLE 1. *Renal Function after Recovery from Renal Failure.*

PATIENT	CAUSE OF ANURIA	AGE	SEX	INTERVAL AFTER ANURIA	SPECIFIC GRAVITY	PHENOLSULFONPHTHALEIN EXCRETION*	INULIN CLEARANCE	PARA-AMINOHIPPURIC ACID CLEARANCE	UREA CLEARANCE	MAXIMUM TUBULAR PARA-AMINOHIPPURIC ACID CLEARANCE	FILTRATION FRACTION
		yr.		mo.		%	ml./min.	ml./min.	ml./min.	mg./min.	
R.A.	Transfusion reaction	47	M	3	1.017	5	58	328	53	57	0.117
				13	1.026	25	67	357	30	60	0.190
C.I.	Transfusion reaction	26	F	3	1.025	20	92	550	57	70	0.165
J.B.	Shock	40	F	34	1.024	25	82	324	49	66	0.259
				55	1.025	25	68	292	40	50	0.230
				76	1.026	25	57	218	39	45	
H.M.	? sulfonamide reaction; ? intravascular hemolysis.	30	F	10	1.024	35	85	372	52	75	0.240
D.T.	Bichloride of mercury intoxication	35	F	12	1.024	35	74	352	47	27	0.214
E.B.	Carbon tetrachloride intoxication	44	F	6	1.026	30	101	423	59	30	0.239
M.R.	Transfusion reaction	25	F	15	1.025	40	86	606	55	40	0.142
I.O.	Shock; transfusion reaction.	27	F	13	1.030	25	63	354	47		0.175
C.R.	Carbon tetrachloride intoxication	32	M	3	1.026	15	78	354	45	60	0.222
				21	1.032	30	82	506	48		0.164
M.O.	Premature separation of placenta	22	F	3	1.024	25	42	226	24	40	0.185
				31	1.024	25	69	260	38		0.265
A.K.	Transfusion reaction	37	F	15	1.024	20	72	269	40		0.267
				27	1.026	25	63	394			0.160
M.B.	Post-partum shock	25	F	15	1.024	20	35	212	30	25	0.165
J.W.	Carbon tetrachloride intoxication	24	M	6	1.026	25	60	280	40	30	0.214
				14	1.030		120	540		80	0.222
R.S.	Intravascular hemolysis	25	M	1	1.032	35	64	480	45	40	0.134
				6	1.030		106	700		80	0.152
E.L.	Shock; trauma.	29	M	6	1.024	25	106	700	60	81	0.152
D.H.	Post-partum shock	32	F	26	1.025	25	100	590	59	83	0.169

*In 15 min.

DISCUSSION

Without determinations of the renal extraction of para-aminohippuric acid the reduced clearance that follows acute renal failure cannot with certainty be interpreted as representing reduced renal blood flow. A subnormal extraction could result in abnormal clearance in the presence of normal renal blood flow. Recent work in which renal blood flow in an anuric human subject was measured by the use of radioactive inert gas suggests that the renal blood flow is truly reduced but to a lesser degree than previous studies using para-aminohippuric acid have indicated.[14]

The interpretation of low inulin clearance is more difficult. Marshall and Hoffman,[7] Redish et al.,[8] Sirota[10] and others have postulated that the renal tubules are abnormally permeable to glomerular filtrate during oliguria and the early recovery phase of acute renal failure. Reduced clearance of inulin may represent either lowered glomerular filtration or back diffusion of inulin or both.

The filtration fraction shows no characteristic alteration in the cases reported. Since the morphologic lesion in the cases studied is thought to be largely tubular, one might expect in theory a glomerular-tubular imbalance, which would be represented by a consistent elevation of the filtration fraction. This was not found, however, and its absence points up the

difficulty of accurately correlating structural and functional changes in renal disease.

Although the present studies showed no correlation between the degree of impairment of residual renal function and the severity or duration of the clinical course of acute renal failure, in an occasional patient prolonged or severe oliguria, particularly when accompanied by recurrent episodes of hypotension and by infection, has apparently resulted in more chronic renal damage than would be expected from study of the 16 cases reported here.

Hyposthenuria is a characteristic phenomenon of the diuretic phase of acute renal failure. Inability to concentrate the urine may persist long beyond return of blood urea nitrogen and serum creatinine to normal values and may be present for a time even when the excretion of phenolsulfonphthalein is normal. Contrary to our earlier clinical impression, however, the present study demonstrates that inability to concentrate does not outlast abnormalities in other parameters of renal function.

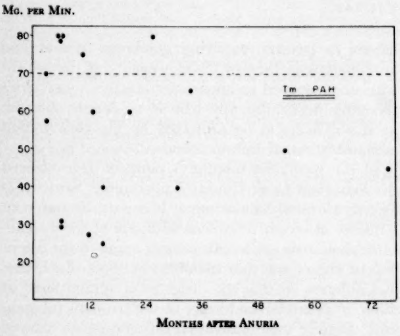

FIGURE 3. *Values for the Tubular Maximum Clearance of Para-aminohippurate at Varying Intervals after the Onset of Acute Renal Failure.*

The dotted line indicates approximately normal values for this laboratory. The range is approximately 75 ± 10 mg. per minute per 1.73 square meters of body-surface area.

Subnormal renal function late in the follow-up period occurred in the majority of cases studied. Although it is not possible to be certain of the exact mechanisms responsible, the findings are of interest and probably represent permanent renal damage after the acute episode. The detailed pathological studies of Oliver et al.[15] have demonstrated that, after acute tubular necrosis, rupture of the basement membrane with abnormal epithelial regeneration may result in the obliteration of whole nephrons and nephron groups, suggesting that function in these units is permanently lost to the kidney. These observations are supported by the subnormal clearance values in the present group of patients. Acute renal failure in patient M.O. occurred under circumstances suggesting bilateral cortical necrosis of the kidneys. Although this syndrome has usually been thought to be associated with a fatal outcome, it is probable that survival after this distinctive lesion depends not on its nature but on its extent, and clinical recovery with some permanent impairment of renal function seems entirely possible. This has been our clinical impression in several cases of acute renal failure and has been suggested by biopsy material in 1 other case.[16]

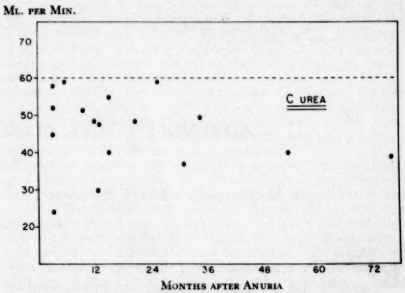

FIGURE 4. *Values for the Clearance of Urea at Varying Intervals after the Onset of Acute Renal Failure.*

The dotted line indicates approximately normal values for this laboratory.

A favorable prognosis is possible after recovery from acute renal failure provided some other pathologic process does not cause additional damage to the kidneys. The progressive decrease of renal function in patient J.B., after the onset of periarteritis nodosa, is an excellent example. Progressive decrease of renal function does not follow recovery from acute renal failure except in situations represented by patient J.B. or with persistent pyelonephritis. Severe pyelonephritis is a frequent complication of acute renal failure from many causes. This indicates the importance of a careful and prolonged follow-up study of all patients who have recovered from acute renal failure.

Summary and Conclusions

Renal function was studied in 16 patients who had recovered from acute renal failure. Within six months, the phenolsulfonphthalein excretion and specific gravity were normal. However, clearance values remained below the lower limit of normal in most patients. These findings are consistent with permanent renal damage of mild degree.

After recovery from acute renal failure, progressive diminution of renal function does not occur unless some other disease causes additional renal damage.

We are indebted to Mrs. Antoinette Dangelo and Miss Virginia Tsiknas for technical assistance.

References

1. Bull, G. M., Joekes, A. M., and Lowe, K. G. Renal function studies in acute tubular necrosis. *Clin. Sc.* **9**:379-404, 1950.
2. Corcoran, A. C., Taylor, R. D., and Page, I. H. Acute toxic nephrosis: clinical and laboratory study based on case of carbon tetrachloride poisoning. *J.A.M.A.* **123**:81-85, 1943.
3. Govaerts, P. Ratio of creatinine clearance to urea clearance in toxic nephropathies. *Stanford M. Bull.* **6**:71-73, 1948.
4. Iseri, L. T., Batchelor, T. M., Boyle, A. J., and Myers, G. B. Studies of fluid, electrolyte, and nitrogen balance in acute renal insufficiency. *Arch. Int. Med.* **89**:188-215, 1952.
5. Lowe, K. G. Late prognosis in acute tubular necrosis: interim follow-up report on 14 patients. *Lancet* **1**:1086-1088, 1952.
6. Luetscher, J. A., Jr., and Blackman, S. S., Jr. Severe injury to kidneys and brain following sulfathiazole administration: high serum sodium and chloride levels and persistent cerebral damage. *Ann. Int. Med.* **23**:741-756, 1943.
7. Marshall, D., and Hoffman, W. S. Nature of altered renal function in lower nephron nephrosis. *J. Lab. & Clin. Med.* **34**:31-39, 1949.
8. Redish, J., West, J. R., Whitehead, B. W., and Chasis, H. Abnormal renal tubular back-diffusion following anuria. *J. Clin. Investigation* **26**:1043-1045, 1947.
9. Reubi, F. Pathogénie de l'insuffisance renale aiguë: causes infectieuses, toxiques, circulatoires: transfusionnelles et traumatiques. *Acta clin. Belg.* **5**:281-344, 1951.
10. Sirota, J. H. Carbon tetrachloride poisoning in man. I. Mechanisms of renal failure and recovery. *J. Clin. Investigation* **28**: 1412-1422, 1949.
11. Schreiner, G. E. Determination of inulin by means of resorcinol. *Proc. Soc. Exper. Biol. & Med.* **74**:117-120, 1950.
12. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Garber, M. Renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. *J. Clin. Investigation* **24**:388-404, 1945.
13. Archibald, R. M. Colorimetric determination of urea. *J. Biol. Chem.* **157**:507-518, 1945.
14. Brun, C., et al. Renal blood flow in anuric human subject determined by use of radioactive Krypton 85. *Proc. Soc. Exper. Biol. & Med.* **89**:687-690, 1955.
15. Oliver, J., MacDowell, M., and Tracy, A. Pathogenesis of acute renal failure associated with traumatic and toxic injury: renal ischemia, nephrotoxic damage and ischemuric episode. *J. Clin. Investigation* **30**:1307-1439, 1951.
16. Crook, A. Communication on necrosis of cortex of kidney after labour. *Proc. Roy. Soc. Med.* **20**:27-38, 1927.

ADRENOCORTICAL STEROIDS AND TUBERCULOSIS*

A Reminder

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RECENT widespread use of the adrenocortical substances has resulted in many optimistic reports regarding their efficacy and clinical applicability. The number of diseases for which these drugs are being given is increasing steadily, and the list of patients who are given courses of treatment with these potent agents is growing daily. Several new products and their derivatives demonstrate greater potency per milligram and are less likely to create electrolyte imbalances. There has been, however, no gross change in the other pharmacologic effects of such drugs. They exert an influence on carbohydrate metabolism, reduce inflammatory reactions, keep fever and its toxic concomitants subdued, give patients a feeling of well-being, deprive the body of its ability to fight infection systemically and suppress local tissue resistance.[1] Several of these effects are of particular importance in tuberculosis. Because of the simultaneous feeling of well-being and the depressed connective-tissue reactivity, it is possible for a tuberculous lesion to spread without producing symptoms.[2] It has been known for a few years that patients with pulmonary tuberculosis who are given corticosteroids may do poorly and show progression of their disease,[2-5] although patients with known tuberculosis who require treatment with these hormones can often be protected by the simultaneous administration of antimicrobials.[6] In fact, there are reports of improved pulmonary lesions in patients receiving combined steroid and antituberculous therapy.[7-9] However, it is the patient with unrecognized or apparently inactive tuberculosis receiving steroid therapy who is in danger, because he is not likely to be protected by the concomitant administration of antimicrobials.

In the past nine months 3 patients have entered the Suburban Cook County Tuberculosis Sanitarium District Hospital-Sanitarium at Hinsdale, Illinois, with a history of recent treatment with one of the adrenocortical steroids. A fourth patient came to the attention of one of the staff members in 1953. Each case was different in that the drugs were administered at different points in the history of the patient's tuberculosis. Despite these individual differences, all showed a definite association between steroid therapy and newly discovered or aggravated tuberculosis. It is hoped that the presentation of these cases will serve as a reminder of the potential dangers that menace patients who harbor a tuberculous infection and are treated with the adrenal hormones. In addition, this paper may alert practitioners to the possibility that clinical tuberculosis can follow steroid therapy in persons who have never shown evidence of the disease.

CASE REPORTS

CASE 1. G.P., a 56-year-old man, had suffered from rheumatoid arthritis for 4 or 5 years. He had received the usual treatment with salicylates, physiotherapy and so forth, but with little beneficial effect. In the spring of 1954 cortisone therapy was started by his doctor at an arthritis clinic. The regimen consisted of 200 mg. of cortisone daily for 2 weeks, followed by a maintenance dose of 50 mg. daily thereafter. X-ray examinations of the chest and sputum studies were performed every 4 months, but no pulmonary disease was ever noted. Early in March, 1955, a productive cough, moderate exertional dyspnea, reduced appetite, fever and

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weight loss developed. The family doctor thought that the patient had a viral pneumonia, and treatment was carried out at home. When the respiratory symptoms did not clear up, an x-ray film of the chest was taken, revealing soft, infiltrating, exudative disease throughout the entire left lung, and scattered infiltrates in the right upper lung. Several sputum specimens were positive on direct smear for acid-fast bacilli. He was admitted to the Hospital-Sanitarium in April with a diagnosis of bilateral, far-advanced active tuberculosis.

Physical examination disclosed a man who appeared acutely ill and moderately dyspneic. Fine rales were heard over the entire left lung, and over the right lung posteriorly. There were deformities of the interphalangeal joints and knees typical of rheumatoid arthritis. Cortisone was stopped, and for several days the patient experienced the symptoms of adrenal insufficiency. He was treated with streptomycin, 1 gm. daily for 2 weeks and then 1 gm. twice weekly for 4 months, when it was necessary to discontinue the drug because of a severe allergic dermatitis. He also received isoniazid, 100 mg. 3 times a day, for the duration of his hospital stay. There was remarkable clinical and radiologic improvement within several months. In fact, his progress was much faster than that usually seen with such extensive disease. After 7 months of treatment he was discharged late in November, when he was greatly improved and smear and culture of the sputum were negative.

Case 2. E.M., a 30-year-old woman, had pulmonary tuberculosis, first diagnosed in 1948. She was hospitalized for 1 year and given bilateral artificial pneumothorax therapy, which was maintained for 5 years. In January, 1955, she complained of a painful right shoulder, and a diagnosis of bursitis was made. After other treatments failed to give relief, she was given cortisone in a dose of 150 mg. daily, with a gradual reduction after 3 weeks and then discontinuation after 1 month. In February a reddish-blue, hot, tender nodule arose between the right breast and the axilla. This was opened surgically, but it continued to drain. At about this time she began to lose weight, a cough developed, and she noticed increasing weakness and fever. By July her cough had become steady and productive, and she had lost 11.3 kg. (25 pounds). X-ray examination of the chest showed a spread of the tuberculosis, and sputum specimens were positive for acid-fast bacilli. (It should be pointed out that she had not received any antituberculous chemotherapy from the time of the initial diagnosis in 1948 until admission in August, 1955.)

Physical examination revealed a cachectic woman, 167.6 cm. (5½ feet) tall and weighing 42.6 kg. (94 pounds), who coughed constantly and appeared chronically ill. Examination of the chest disclosed dullness over the right apex and crepitant rales over both upper-lung fields. There was a draining sinus just above and lateral to the right breast. Smears taken from the sinus revealed many acid-fast bacilli.

After admission, she received streptomycin, 1 gm. twice weekly, and isoniazid, 100 mg. 3 times a day. She became afebrile and gained about 4.5 kg. (10 pounds), and smears became negative. However, sputum cultures are still positive for acid-fast bacilli.

Case 3. M.F., a 35-year-old woman, was first known to have tuberculosis about 20 years before admission, when her father and sister also had this disease. At that time she received no specific therapy, but apparently recovered and remained symptom free over the years. She was followed periodically at a chest clinic with roentgenograms and sputum examinations. X-ray studies in 1951 and 1952 revealed a stable apical lesion on the right; sputum studies in the same years were negative on smear and culture for acid-fast bacilli. In the last week of February, 1953, pain developed in the proximal interphalangeal joints of the hands as well as in both elbows, and a course of cortisone was started. The dose was 100 mg. daily for 2 days, 50 mg. daily for 3 days and then 25 mg. daily for 4 to 6 weeks. In March, about 4 weeks after the initiation of cortisone therapy, a febrile illness diagnosed as influenza developed. However, x-ray examination showed a definite spread of the tuberculosis, with a cavity in the right apex. The sputum specimens were positive for acid-fast bacilli.

She was admitted to a sanatorium on April 11 and treated with a 90-day course of streptomycin, 1 gm. 3 times a week, and para-aminosalicylic acid, 10 gm. daily. Isoniazid, 100 mg. 3 times a day, was started on June 23. A modified thoracoplasty with a paraffin pack was done in June. She was discharged at the beginning of August, and continued on isoniazid and para-aminosalicylic acid therapy for 13 months. At present she is working and asymptomatic. Sputum specimens have remained negative on smear and culture.

Case 4. E.A., a 65-year-old woman, became ill with rheumatoid arthritis 13 years before admission, with gradual involvement of many joints. She had received intermittent salicylate therapy and in recent years had been given phenylbutazone, with little benefit. In May, 1955, about 6 months before admission, a cough, which was dry at first but then became productive, developed. Her appetite became poor, and she started to lose weight. She grew very weak and tired easily. In the latter part of July, 1955, a doctor placed her on prednisolone therapy for arthritis, prescribing a dose of 5 mg. 3 times a day for 30 days. At that time she began to feel progressively worse, had an increase in cough and on 1 occasion brought up some blood clots in the sputum. In October x-ray examination (performed for the 1st time in her life) disclosed a lesion in the left-middle-lung field. Sputum specimens were obtained, and 3 were positive for acid-fast bacilli on direct smear. She was admitted to the Hospital-Sanitarium in November.

Physical examination revealed a woman who was pale and obviously chronically ill. Examination of the chest was not remarkable. A soft systolic murmur was heard at the apex. The fingers and toes had typical rheumatoid deformities. Both knees were swollen, and she could not raise her arms above the horizontal position. Several subcutaneous nodules were present about the elbows. At present she is receiving streptomycin, 1 gm. twice weekly, and isoniazid, 100 mg. 3 times a day. She has been on treatment for 7 weeks and seems to be making satisfactory progress.

Discussion

Reports published when cortisone and ACTH were first being used on a large scale clearly pointed out that tuberculosis can follow therapy with these drugs.[10-12] It was also noted that tuberculous patients responded to the steroids with defervescence, increased strength, improved appetite, weight gain and a subjective feeling of well-being. At the same time, however, most showed no improvement or progression of lesions on x-ray study, and when the drugs were stopped, the symptoms returned. In 1952 the Committee on Therapy of the American Trudeau Society prepared a statement in which the following conclusions were reached[13]: cortisone and ACTH therapy may reduce the signs and symptoms of tuberculous disease even when the net effect of such treatment is harmful; this therapy may cause exacerbations of active or apparently inactive tuberculosis; and cortisone and ACTH tend to cause poor localization of tuberculous disease and to facilitate widespread dissemination. As a result of the evidence then available, the Committee made the following recommendations: the presence of old, apparently inactive tuberculosis should be carefully evaluated for activity before hormone therapy is started, and frequent follow-up x-ray examinations and sputum studies should be made after such treatment is instituted; and, even in the absence of known tuberculous infection, x-ray examination of the chest before, during and after hormone therapy is wise. Although the entire problem deserves reconsideration in the light of more recent

studies, it seems prudent to follow the recommendations made above when one is planning to initiate therapy with ACTH or one of the adrenal steroids.

Among the cases presented in this report three different situations are worthy of note. In Case 1 the patient had no evidence of tuberculous disease at the start of cortisone therapy. Management during treatment must be considered unusually careful in that he was seen frequently at the clinic and had periodic x-ray examinations of the chest and sputum studies. Despite the awareness of the dangers involved and the excellent care he received, he was eventually found to have fulminating pulmonary tuberculosis. Thus, it is apparent that even when there is no reason to suspect tuberculosis and when medical supervision is meticulous, frank disease can follow therapy with cortisone.

Cases 2 and 3 represent what we considered to be reactivations of inactive tuberculosis. In 1 patient not only did the size of the pulmonary lesions increase but also a tuberculous abscess developed and formed a chronic draining sinus after surgical incision. This implies a breakdown of body defenses sufficient to permit the seeding of the infection into a new anatomical site. In the other patient, who had had no trouble for twenty years, a cavitary lesion developed — a result commonly reported after steroid therapy. Although these reactivations do not necessarily implicate the adrenal steroids as the only causative factor, the close association observed certainly suggests that they were responsible for these exacerbations. This point of view is strengthened by the fact that nothing else could be detected in the histories to account for the reactivations.

Case 4 probably represents a patient who was given an adrenal steroid after the tuberculosis had become active. Although clinical reports are somewhat conflicting in this matter, in that some patients in this situation showed improvement or no change and others had unfavorable responses,[8] it seems likely that this patient was made worse clinically, as indicated by the rapid progression of her symptoms.

At present there are no accurate statistics available on the percentage of patients receiving steroids who show development or reactivation of tuberculous lesions. Even if the proportion is small, the actual number may be significant because of the huge population involved. Therefore, the situation creates a potentially important public-health problem. It is not suggested that the adrenal steroids are being prescribed excessively or promiscuously; rather, it is hoped that they will be used with full recognition of their potential complications. We believe that any person who is to receive treatment with the steroids should be thoroughly investigated for the presence of active or inactive tuberculosis. If such disease is detected, and treatment with one of these agents is unequivocally indicated, the patient should be protected with the simultaneous administration of antituberculous medication. In cases in which no evidence of tuberculosis exists, the patient should be followed carefully and have an x-ray examination of the chest at least every two months. In addition, if the patient is initially Mantoux negative, periodic tuberculin testing may be of value.

Summary and Conclusions

Four cases in which the adrenocortical steroids were instrumental in the development, reactivation or aggravation of pulmonary tuberculosis are presented. It is probable that many other such cases have occurred. The taking of a detailed history and periodic x-ray studies of the chest would doubtless reduce such events to a minimum. If patients with active or inactive tuberculosis require steroid therapy, they should be safeguarded by the concomitant administration of antimicrobials and meticulous clinical observation. Those who have never had recognized tuberculosis need initial and frequent follow-up roentgenograms during treatment with these hormones.

References

1. Goodman, L. S., and Gilman, A. *The Pharmacological Basis of Therapeutics: A textbook of pharmacology, toxicology, and therapeutics for physicians and medical students.* Second edition. 1831 pp. New York: Macmillan, 1955.
2. Des Autels, E. J., Zvetina, J. R., and Freeman, S. Effects of corticotropin (ACTH) and cortisone in fifteen cases of pulmonary tuberculosis. In *Transactions of the Fourteenth Conference on Chemotherapy of Tuberculosis: Held on February 7 through 10, 1955 at the Fulton County Medical Society, Atlanta, Georgia by the Veterans Administration: Army: Navy with the cooperation of the National Tuberculosis Association.* 556 pp. Washington, D. C.: Veterans Administration Area Medical Office, Atlanta, Department of Medicine and Surgery, 1955. Pp. 296-298.
3. Traut, E. F., and Ellman, J. Exacerbation of tuberculosis during treatment with cortisone. *J.A.M.A.* **149**:1214-1218, 1952.
4. Capon, A. W. ACTH, cortisone and tuberculosis. *Canad. M. A. J.* **62**:46-48, 1952.
5. Editorial. Deleterious effects of ACTH and cortisone on tuberculosis. *New. Eng. J. Med.* **245**:662-664, 1951.
6. Houghton, L. E. Combined corticotrophin therapy and chemotherapy in pulmonary tuberculosis, with special reference to hypersensitive reactions. *Lancet* **1**:595-598, 1954.
7. Cochran, J. B. Cortisone in treatment of pulmonary tuberculosis. *Edinburgh M. J.* **61**:238-249, 1954.
8. Johnson, J. R., and Davey, W. N. Cortisone, corticotropin, and antimicrobial therapy in tuberculosis in animals and man: review. *Am. Rev. Tuberc.* **70**:623-636, 1954.
9. Sors, C., Roujeau, J., Trocmé, Y., and Testard, R. Indications et résultats du traitement des tuberculoses séreuses et de la tuberculose pulmonaire par l'A.C.T.H. associé aux antibiotiques. *Rev. de la tuberc.* **18**:522-543, 1954.
10. King, E. Q., Johnson, J. B., Batten, G. S., and Henry, W. L. Tuberculosis following cortisone therapy: report of case of rapidly progressive pulmonary tuberculosis following cortisone therapy for rheumatoid arthritis. *J.A.M.A.* **147**:238-241, 1951.
11. Fred, L., Levin, M. H., Rivo, J. B., and Barrett, T. F. Development of active pulmonary tuberculosis during ACTH and cortisone therapy. *J.A.M.A.* **147**:242-246, 1951.
12. Popp, C. G., Ottosen, P., and Brasher, C. A. Cortisone and pulmonary tuberculosis. *J.A.M.A.* **147**:241, 1951.
13. American Trudeau Society. Effect of cortisone and/or corticotropin on tuberculous infection in man: statement prepared by Committee on Therapy. *Am. Rev. Tuberc.* **66**:254-256, 1952.

MEDICAL PROGRESS

REGIONAL ENTERITIS (Concluded)*

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THERAPY

In the absence of a specific etiologic agent responsible for the disease, medical management is empirical and symptomatic. Spontaneous resolution is rare except in the early acute, uncomplicated stage found incidentally at operation. In this circumstance, when an acute process is recognized, in the absence of any chronic underlying disease, clinical and even pathological remission is frequent enough to warrant avoidance for the time being of any further definitive surgical treatment, such as sidetracking or resection. In most cases, however, by the time the diagnosis has become definitely established, the pathological changes have progressed beyond this early acute phase into the cicatricial stenosis, or the tubular cast due to widespread mucosal ulceration and destruction, characteristic of long-standing enteritis. It is to this group of chronic enteritis in its static or progressive forms with acute exacerbation that the major therapeutic efforts are directed.

Sufficient time has elapsed to evaluate the efficacy of various measures, and several generalizations can be safely made. No therapy is curative. No regimen, medical or surgical, is so universally effective as to warrant its acceptance over others, except in the presence of certain complications. Medical therapy is expectant and supportive and, in general, indicated in the care of acute enteritis, chronic enteritis without complications, diffuse ileojejunitis and recurrent disease. Surgical treatment, with few unpredictable exceptions, has hardly fulfilled its original promise: "all patients who survive operation being alive and well."[1] It is now undertaken to effect palliation and control in the presence of obstruction, perforation with peritonitis, fistulas and a large, tender abdominal mass, and when conservative medical measures have failed to prevent invalidism.

The effectiveness of any new measure must be evaluated in the light of the possibility of spontaneous improvement, and the poor correlation, at times, between the clinical status, roentgenographic picture and pathological findings. The roentgenographic interpretation of recurrence, by itself, is no more an indication for further surgery than the clinical remission is necessarily an accurate reflection of the underlying histology.

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The major therapeutic measures advanced, supported and in some cases eventually abandoned are reviewed below in detail.

General Medical Measures

Conservative medical management is aimed at maintaining nutrition, allaying diarrhea, restoring blood lost and controlling infection. Optimal dietary needs are best met with a high-calorie, low-residue, nonirritating diet from which specific elements such as milk and milk products may be omitted on the basis of observed intolerance. The amount and method of administering essential and accessory food factors must be computed on the basis of increased loss and need, as well as the diminished absorptive capacity of the involved gut. Extreme degrees of malnutrition and debility are most frequently observed with recurrences after surgery, though they may represent the failures of medical management for which the original operation was undertaken.

X-Ray Therapy

In conjunction with other nonspecific measures, x-ray therapy has been used primarily in severe and progressive disease when the patient's general condition or the extensiveness of the involvement precludes resection. Similarly, when recurrences after successive resections militate against further surgery, attempts have been made to control the active process by diffuse radiation over the abdomen. The over-all results are not encouraging, an increase in fever, bleeding and stenosis being produced in some cases.[52]

Chemotherapy

As with ulcerative colitis, chemotherapeutic agents have been disappointing when applied in the active, febrile stage, except in relation to purulent complications. The enthusiasm that heralded the advent of each new antibiotic drug has not stood up to the test of time, and their use has occasionally been associated with a severe pseudomembranous enteritis, clinically similar to the disease being treated. The nonabsorbable sulfonamides are most appropriate, since they may be used over a long period with relative safety and effectiveness. The beneficial responses observed cannot be correlated with the bacterial cultures and sensitivity reactions.

Steroid Therapy

The unsatisfactory status of therapy for regional enteritis was an obvious challenge and stimulus to the use of ACTH, cortisone and related compounds. In common with ulcerative colitis, its similarity in several aspects (arthralgia and erythema nodosa) to states in which these drugs have been effective — rheumatic fever and rheumatoid arthritis — provided a scientific basis for their therapeutic application. The results obtained have in large part been due to the improvement in mood and appetite, and consequently in nutrition. Their possible inhibition of the inflammatory response, with consequent reduction in the tendency to fibrosis and stenosis, has been offset by the occasional catastrophe of frank perforation with peritonitis. As in many other conditions, these drugs may be followed by a dramatic remission in fever, diarrhea and weight loss. This improvement is of unpredictable duration, but may be maintained in some cases by continued administration in small doses over a period of many months. Objectively, the roentgenographic appearance of the involved bowel does not reflect for some time, if ever, the favorable clinical response. These preparations are not curative and may be followed by serious complications such as perforation, bleeding, electrolyte and mental disturbances, among others. Although important adjuncts, they should not be considered definitive substitutes for all other projected methods of treatment.[52-56]

Surgical Treatment

The indications for surgical intervention have described a complete circle. The first surgical specimens available for systematic study, before the true nature of regional enteritis was recognized, were obtained during the course of treatment for obvious surgical conditions — obstruction, perforation, intra-abdominal masses and fistulas. For a short time after 1932, the original dictum about the curative value of definitive resection held sway — "the proper approach to a complete cure is by surgical resection of the diseased segment of the small intestine and of the ileo-cecal valve with its contiguous cecum."[1] The importance of recognizing the disease early, so that the lesion could be removed before complications set in, emphasized the value of early roentgenographic observations and helped establish diagnostic criteria. With the recognition of the morbidity, mortality and recurrence rate after any type of surgical procedure, the earlier enthusiasm waned. The major indications for more radical therapy have reverted to the very complications that produced the first gross examples of the disease. There is now agreement that the diagnosis of regional enteritis does not immediately or even inevitably lead to surgery, and that even radical resection, removing all the obviously involved bowel and lymph nodes, may not be curative.

The major differences of opinion thus revolve not around the part played by the surgeon, or even when he is to make his entry into the surgical amphitheater, but the manner in which he is to wield his scalpel.

The evolution of the various surgical procedures began with the excision of the grossly abnormal segment of bowel, progressed to the accomplishment of essentially the same resection as a two-stage operation, after a preliminary sidetracking ileocolostomy, and culminated in the use of the defunctioning ileocolostomy as the only measure necessary.[58]

These major divisions of surgical therapy all have their individual proponents, with arguments both theoretical and pragmatic.[59-61] The excision of an inflamed portion of bowel is founded on the sound surgical principle of removing from the abdominal cavity obvious pathologic bowel already producing various complications and capable of precipitating progressive ulceration, obstruction and perforation even within the excluded bowel, unless it is resected. The opponents of this view point to an increased surgical mortality in the one-stage procedure and a recurrence rate no better than that obtained with less radical measures, and are skeptical about the advisability and feasibility of removing all pathologic lymph nodes and bowel on the basis of gross inspection alone.[58,62]

Those who adhere to the use of ileocolostomy, after excluding the proximal end of the involved intestine, refer to their previous experience with the two-stage procedure, when, on re-entering the abdomen to resect the bowel after an earlier sidetracking, they frequently found marked resolution of the active process.[58] The lower morbidity and mortality, without any worsening of the recurrence rate in this most conservative of the more commonly employed types of surgery, have strengthened the faith of its advocates in its value above the others.

Unfortunately, as with many similar controversies, the surgical results are subject to various interpretations and differ considerably in clinics employing similar technics. The optimistic views held by the proponents of one form of approach cannot be confirmed by a perusal of published statistics (Table 1). The length of the follow-up period and the completeness with which such studies are made are directly reflected in the recurrence rate, which increases the longer one waits after surgery of all types.[58] Patients lost to follow-up survey may have succumbed to the disease or transferred their problems to the care of others. Unless this group is considered under the heading of poor results, the significance of the results may be unjustifiably and incorrectly weighted. Table 1 refers to representative results, in terms of mortality and recurrences, gleaned from the current literature on this topic, and suffers from the fact that reference is seldom made to the length of follow-up study or the indications for surgery and the stage at which it was undertaken. Nor is the distinction always made between evidence of recurrence on the x-ray film and that based on clinical results alone. In some series, recurrence was seen on x-ray examination in more

than 50 per cent of patients observed for at least five years after being subjected to all types of surgery, and yet the clinical results in over 75 per cent were considered satisfactory.[63]

TABLE 1. *Mortality and Recurrence.*

SOURCE OF DATA	RESECTION		ILEOCOLOSTOMY	
	MORTALITY	RECURRENCE	MORTALITY	RECURRENCE
	%	%	%	%
Garlock et al.[58]	14.0	46.0	0	22.8
Kiefer[64]	2.0	34.0	—	—
King et al.[65]	11.2	21.9	4.6	28.9
Bockus & Lee[2]	—	46.0	—	—
Van Patter[52]	—	67.0	—	57.0

It is this high recurrence rate, even in the hands of the most enthusiastic sponsors of any one form of operation, that has relegated surgery to the role of a palliative rather than curative measure. This disappointing aspect is usually found within a year of operation, at the proximal point of the new anastomosis — the "new terminal ileum."[64]

The explanations for such a sequel rest on several theoretical assumptions as well as some retrospective observations. Before intermittent or skip areas of ileal and jejunal involvement were recognized as distinct possibilities, to be looked for and taken into account in the placing of the ileocolostomy, segments of actively diseased bowel were undoubtedly incorporated into the new anastomosis or left intact just proximal to it.[53] Even now it may be difficult to determine the presence of mucosal and submucosal disease when it is viewed from the serosal surface. On more theoretical grounds, the multicentric or diffuse origin of the enteritis would explain the recurrence as a recrudescence from residual foci, unrecognized even on biopsy examination.[57] When the operation is limited to a sidetracking without resection, there may be persistence rather than recurrence of activity — an eventuality found in almost half the patients so treated.[33] The relief obtained clinically is not always an accurate reflection of the satisfactory removal of all disease. Unfortunately, once the disease has recurred, there is an ever-increasing frequency of further recurrence after each attempt at surgical therapy.[65]

The nutritional effects noted after bowel resection in regional enteritis have been thoroughly studied.[66] This problem is compounded of many facets. The first is the poor nutritional status of the patient before surgery because of fever, diarrhea, inadequate intake and malabsorption, excessive loss of blood and protein in purulent exudates and of essential foodstuffs in diarrhea. The second is the loss of absorptive area in the resected or defunctionalized small intestine; whereas the amount usually resected is theoretically compatible with normal absorption in the remaining bowel, such a generalization holds only when the residual bowel is functionally sound and intact, as after resection of the bowel for mesenteric thrombosis, trauma or tumor. Thirdly, not only does one start off with an impoverished nutritional status before surgery but also the remaining bowel already suffering from impaired absorptive capacity secondary to a chronic deficiency state[67] is often found to be the seat of a recurrent or persistent inflammatory process. The presence of this actively diseased portion of bowel is more important than the length of segment removed in affecting nutrition adversely. Conversely, nutrition improves even with the removal of a large segment of diseased bowel if the remaining, relatively small portion of the bowel is normal.

Disturbances in absorption of carbohydrates, proteins and fats are manifested in flatulence, edema and loss of fat-soluble vitamins, respectively, as well as secondary anorexia, weight loss, hypocalcemia, bleeding tendencies and tetany. Treatment of these deficiencies may require the parenteral use of fat-soluble and water-soluble vitamins, transfusions of whole blood and albumin fractions, and sufficient fat to make the diet palatable. The efficacy and limitations of medical and surgical therapy have been discussed by Crohn and Janowitz[68] and by Janowitz.[69]

SUMMARY AND CONCLUSIONS

In the twenty-five years that will soon have elapsed since regional ileitis made its debut on the medical scene, progress has been made in establishing its physical boundaries and clinical features and in evaluating the respective roles and limitations of medical and surgical therapy.

The pessimism and disillusionment about the effectiveness of any regimen in providing more than palliation and control of symptoms and complications must be tempered by the realization of its relatively recent status. This question may not be fully resolved until therapy follows advances in etiology.

Experimental efforts thus far have indicated various approaches along the pathway leading to granulomatous disease of the bowel. Though this is a clinical and apparently pathological entity, the primary etiologic factors may be heterogeneous. Certainly, no single cause has been described that can be considered responsible in all cases of regional enteritis.

As with many conditions of unknown etiology, therapy remains conservative and supportive, surgical intervention being limited to various complications and progressive intractability.

The relative merits of any objections to the several accepted methods of surgical therapy are briefly noted. They all suffer from the disappointing sequel of recurrence or persistence of the disease. The more favorable results after surgery for the fixed stenotic lesion are in contrast to those obtained in the nonobstructive, nonperforating, progressively ulcerating phase.

The varying picture and therapeutic approach applicable to the different subgroups of regional enteritis, such as acute ileitis, ileojejunitis, duodenitis and ileocolitis, are considered.

The nutritional disturbances consequent to extensive disease, especially in association with recurrent activity after surgical procedures, their pathogenesis and treatment, are discussed in relation to diminished intake, increased loss and decreased absorptive capacity.

References

52. Gray, S. J., Reifenstein, R. W., Benson, J. A., Jr., and Young, J. C. Treatment of ulcerative colitis and regional enteritis with ACTH: significance of fecal lysozyme. *Arch. Int. Med.* **87**:646-662, 1951.
53. Kirsner, J. B., Palmer, W. L., and Klotz, A. P. ACTH in severe chronic regional enteritis: : observations in 4 patients. *Gastroenterology* **26**:229-233, 1952.
54. Machella, T. E., and Hollan, O. R. Effect of cortisone on clinical course of chronic regional enteritis and chronic idiopathic ulcerative colitis. *Am. J. M. Sc.* **221**:501-507, 1951.
55. Sauer, W. G., Brown, P. W., and Dearing, W. H. Experience with use of corticotropin in regional enteritis. *Gastroenterology* **22**: 550-563, 1952.
56. Stanley, M. M., Rosenberg, I. N., and Cleroux, A. P. Use of corticotropin (ACTH) in treatment of chronic regional enteritis. *M. Clin. North America* **35**:1255-1265, 1951.
57. Ginzburg, L. Surgical treatment of regional enteritis. *J. Mt. Sinai Hosp.* **22**:215-222, 1955.
58. Garlock, J. H., Crohn, B. B., Klein, S. H., and Yarnis, H. Appraisal of long term results of surgical treatment of regional ileitis. *Gastroenterology* **19**:414-423, 1951.
59. Marshall, S. F. Chronic regional ileitis: resection of diseased intestine rather than ileocolostomy. *Lahey Clin. Bull.* **8**:66-70, 1953.
60. Lewisohn, R. Segmental enteritis. *Surg., Gynec. & Obst.* **66**:215-222, 1938.
61. Maxeiner, S. R. Ideas of surgical management of regional enteritis. *Arch. Surg.* **66**:884-887, 1953.
62. Starr, A. Is there adequate therapy for regional enteritis? *Surg., Gynec. & Obst.* **87**:351, 1948.
63. Dyson, W. L., Hodes, P. J., and Rhoads, J. E. Late results in surgical treatment of regional enteritis. *Pennsylvania M. J.* **57**: 433-438, 1954.
64. Kiefer, E. D. Recurrent regional ileitis. *Lahey Clin. Bull.* **8**: 149-156, 1953.
65. King, F. H., et al. Inflammatory diseases of gastrointestinal tract: clinical conference. *J. Mt. Sinai Hosp.* **20**:58-71, 1953.
66. Kiefer, E. D., and Arnold, W. T. Nutritional problems following resection of small intestine for regional ileitis. *J.A.M.A.* **144**:903-909, 1950.
67. Zetzel, L., Banks, B. M., and Sagall, E. Intestinal absorption of amino-acid mixture in patients with chronic idiopathic ulcerative colitis and enterocolitis. *Am. J. Digest. Dis.* **9**:350-352, 1942.
68. Crohn, B. B., and Janowitz, H. D. Reflections on regional ileitis, twenty years later. *J.A.M.A.* **156**:1221-1225, 1954.
69. Janowitz, H. D. Problems of regional ileitis. *J. Mt. Sinai Hosp.* **22**:223-228, 1955.

MEDICAL INTELLIGENCE

BENIGN DUODENOCOLIC FISTULA*

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BOSTON

ALTHOUGH duodenocolic fistulas due to carcinoma are common, we have been impressed by the paucity of reports concerning this condition in benign disease. The following case is therefore believed to be of interest.

Case Report

L.J. (P.H. #32316), a 39-year-old Negro, was admitted to the hospital on July 14, 1952. He had been studied at a general hospital in June because of gnawing epigastric pain and the presence of anemia (the hemoglobin was 3.7 gm. per 100 ml.). He was given a transfusion. An upper gastrointestinal series reportedly showed a defect of the prepyloric area. Barium-enema examination revealed deficient filling and irregularity of the medial aspect of the hepatic flexure. These findings were thought to be due to adjacent tumor, and the patient was referred to the Pondville Hospital.

The epigastric pain had gradually appeared over a 2-year period, with recent increase in severity. The pain radiated through to the back, but not into the shoulders, and usually occurred between meals and was relieved by milk and food. There was no history of night pain. In recent months, milk, alkali and food gave only minimal relief. There was a recent history of minimal vomiting of watery gastric material, but no hematemesis. In the month before admission, the weight had dropped from 72.6 kg. (160 pounds) to 63.5 kg. (140 pounds). The patient had smoked a maximum of ½ package of cigarettes a day. Alcoholic intake was denied. The past and family histories were noncontributory.

Physical examination revealed a well developed man in slight distress. The abdomen was not distended. There was moderate tenderness in the right upper quadrant, extending into the epigastrium. Several examiners felt an ill defined mass in the right upper quadrant, but it could not be delineated. There was moderate rigidity in the right upper quadrant of the abdomen, but no spasm.

Examination of the blood showed a red-cell count of 3,400,000, with a hemoglobin of 7.9 gm. per 100 ml. The stools gave +++ tests for occult blood. Gastric analysis revealed fluid that was guaiac negative, with 57° of free hydrochloric acid in a fasting specimen; after histamine, free hydrochloric acid rose to 100°.

Intravenous pyelography disclosed normal upper urinary tracts. Barium-enema study revealed an irregular filling defect in the region of the hepatic flexure, with partial obstruction to the flow of barium. An upper gastrointestinal series showed a filling defect of the distal portion of the stomach. Peristaltic waves did not pass through this area, and there was evidence of almost complete obstruction in the 2d portion of the duodenum. The radiologic diagnosis was an extrinsic mass associated with the distal end of the stomach and duodenum, as well as the colon, probably secondary to the perforation of a malignant tumor involving the distal portion of the stomach. A cholecystogram was unsuccessful because dye from the gastrointestinal tract was not absorbed.

The patient received 6 transfusions (3000 ml.) of whole blood and was prepared for surgery. On July 28 laparotomy by one of us (E.M.D.) revealed a large mass involving the distal end of the stomach and duodenum, extending up under the liver and involving the hepatic flexure. The hepatic flexure was separated from the mass, demonstrating a perforation in the hepatic flexure of the colon and in the adjacent anterior and superior aspects of the 2d portion of the duodenum (Fig. 1). There was an abscess beneath the left lobe of the liver, which was later drained. The hepatic flexure was freed up, and a segmental resection was done with an end-to-end anastomosis. The large defect in the duodenum was closed and covered with a segment of omentum. The gall bladder could not be visualized. An anterior gastrojejunostomy was carried out. The incision was closed with drainage.

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Pathological examination revealed a segment of colon, 16 cm. in length. The serosa was thickened and edematous. It presented the crater of a large ulcer, 5 cm. in diameter, with the perforation 1 cm. in main diameter. Microscopical examination revealed that this could have been due to peptic ulceration penetrating the colon.

The postoperative course was surprisingly uncomplicated, considering the degree of inflammatory disease present. The patient was discharged on the 16th postoperative day.

When he reported for follow-up study on September 9, 1954, he weighed 61.2 kg. (135 pounds) — slightly less than he had before operation. In November, barium-enema study showed a normal-appearing colon. There was no fistulous tract. An upper gastrointestinal series revealed a functioning gastrojejunostomy, but there was an ulcer crater in the jejunum, 1.3 by 0.5 cm., directly opposite the site of the stoma. He was placed on an ulcer regimen. In April, 1955, he weighed 67.1 kg. (148 pounds). He admitted that he had not followed the ulcer regimen. Arrangements were made for repeat x-ray examination, but he failed to return for further study or treatment.

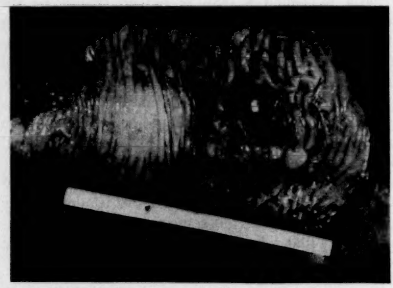

FIGURE 1. *Resected Segment of the Colon, Showing the Mucosal Surface, with the Fistulous Opening.*

DISCUSSION

This is the seventh case reported in which there has been a duodenocolic fistula secondary to peptic ulceration of the duodenum. McPeak[1] presented 2 cases, and single case reports were made by McClinton,[2] Krock,[3] Railton[4] and Rife.[5]

Although these findings are seen more often with duodenal ulcer, it has been reported with other benign conditions. Rees[6] is credited with the first report of a case of duodenocolic fistula associated with benign disease (1933); in that case there was also an incompetent sphincter of Oddi. The patient, a sixty-two-year-old woman, was thought to have had a perforation of a typhoid ulcer in an attack twenty-eight years previously. Ogilvie's[7] 2 cases were secondary to caseating tuberculous lymph nodes. Ormandy and Bargen[9] reported a case with cologastric and coloduodenal fistulas secondary to thromboulcerative colitis that was studied at autopsy. Ransom[10] added 2 cases due to ulcerative colitis. Neville[11] described a case secondary to acute cholecystitis. Thus, 14 cases of duodenocolic fistula associated with nonmalignant conditions have been reported.

Although diarrhea is a prominent symptom in most cases, it was not seen in the present case. The fistula is usually demonstrated by barium-enema study and seldom shown by upper gastrointestinal series. In the case presented above, the fistula was not demonstrated radiographically. This may have been due to the considerable inflammatory reaction present as well as the partial obstruction of both duodenum and colon. When obstruction is not present, the patient has increased appetite but nevertheless loses weight. There have been no reports of foul vomitus, as frequently seen with gastrocolic fistula. But the problems of nutrition in these patients closely parallel those seen with gastrojejunocolic fistula.

SUMMARY

A case of duodenocolic fistula due to benign disease is presented. In this case the etiology was peptic ulceration of the duodenum. This is the seventh case of duodenocolic fistula with this etiologic background that has been reported.

REFERENCES

1. McPeak, C. N. Benign duodeno-colic fistula, with report of two cases. *Radiology* **34**:343-350, 1940.
2. McClinton, J. B. Non-malignant duodeno-colonic fistula. *Canad. M. A. J.* **1**:434-436, 1944.
3. Krock, F. Discussion of Ogilvie.[7]
4. Railton, S. V. Benign duodeno-colonic fistula. *Canad. M. A. J.* **58**:267, 1948.
5. Rife, C. S. Benign duodenocolic fistula. *Arch. Surg.* **62**:876-882, 1951.
6. Rees, C. E. Duodenocolic fistula with incompetent sphincter of Oddi. *J.A.M.A.* **100**:496, 1933.
7. Ogilvie, H. Non-malignant duodeno-colic fistula: report of 2 cases. *Ann. Surg.* **131**:899-902, 1950.
8. Winfield, J.M. Discussion of Rife.[5]
9. Ormandy, L., and Bargen, J. A. Thrombo-ulcerative colitis associated with cologastric and coloduodenal fistulas. *Proc. Staff Meet., Mayo Clin.* **14**:550-552, 1939.
10. Ransom, H. K. Discussion of Rife.[5]
11. Nevile, W. E. Duodenocolic fistula due to acute cholecystitis. *Am. J. Surg.* **87**:300-302, 1954.

BY THE LONDON POST

Marriage and Divorce — Doctors and Advertising — Searching for the Virus

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LONDON, ENGLAND

IN England and Wales in 1954, there were 27,471 divorces, compared with 4735 in 1937. This high incidence of broken marriages is a matter of concern to all who are interested in the stability of modern society, and the Royal Commission on Marriage and Divorce, appointed in 1951, has just published its report.

The Commission has pointed out that the social and economic emancipation of women has enhanced the quality expected of marriage and at the same time has created new strains and added to the risk of breakdown. Nevertheless, in countries where the focal point of society is still the family unit, one must accept the principle that marriage, except for grave reasons, is indissoluble; otherwise, many children are likely to be denied the security and affection of a home that are so vital for their satisfactory upbringing. Indeed, the Commission has stressed the fact that every year some 20,000 children under sixteen are being affected by the divorce of their parents.

Throughout its deliberations, therefore, the Commission has been mindful of the importance of preventing the breakdown of marriages and has considered the best methods of prevention, urging an extension of the marriage-guidance services and suggesting that more generous allocations be made from public funds for their work. It has also urged that every effort be made at conciliation and suggested that the conciliation work of the probation service be extended.

Several medical aspects of marriage were considered by the Commission. In particular it discussed the problems raised by artificial insemination and by the mental illness of a spouse. The Commission considered that the acceptance by a wife of artificial insemination by a donor without the husband's consent should be recognized as a ground for divorce since it involves the fathering of a child on the husband without his knowledge. On the other hand the Commission did not consider that the agreed acceptance of artificial insemination by both parties should be grounds for either party to seek to nullify the marriage. Another new suggested ground for divorce is the detention in an institution for five years of a spouse who is a mental defective with dangerous or violent propensities. The Commission also recommended that when a spouse is incurably of unsound mind and has been continuously under care and treatment for five years there is adequate ground for divorce.

Other medical problems considered included the effects of sexual deviations in relation to marriage and of such conditions as habitual drunkenness, venereal disease and epilepsy. The Commission also discussed the implications of the willful refusal to consummate the marriage or to have a child, but no firm agreement was reached on when these various conditions should be grounds for divorce.

Throughout the report the Commission laid worthy stress on the view that efforts should be aimed at the prevention of marital breakdown. On the other hand it seems doubtful whether the true etiology of a prevalent disease of the time has been discovered.

* * *

To maintain the traditional ban on advertising in any form, for which a doctor may render his name liable to erasure from the Medical Register, the ethical committee of the British Medical Association advised that any physician taking part in either sound or visual broadcasting should insist on anonymity as part of his contract. This advice has caused adverse comment from some members of the public, who already find difficulty in understanding the principles of medical ethics.

The lay public, with an ever-increasing desire for medical knowledge and with the availability of increasingly efficient means of communication, tends to resent the fact that the face on the television screen, or the voice at the microphone, must remain anonymous. It is claimed that without a name the information offered lacks a certain authority. Although this complaint may have a certain slight justification, the *British Medical Journal* points out that the leading national newspapers have printed medical articles by anonymous writers for many years, the newspapers themselves taking the responsibility for authority. Furthermore, the disadvantage of allowing medical men to broadcast under their professional names is mentioned. It is easy to understand how a man might appear as the leading specialist in his field after a television program in which he took the leading part, thereby gaining professional advantage over his colleagues. It is contended that this is not the way in which a professional man should reach pre-eminence in his field. His judges should be his informed colleagues and not an uninformed lay public. The criteria by which a man is judged should be the standard of his published work, his practice and his contributions to medical discussions and not the standard of his performance on the television screen or in front of the microphone.

In a leading article the *British Medical Journal* stressed the importance of the principle involved in such matters as these. Some members of the medical profession might consider it easy to yield to public pressure which clamors for sensation and personal publicity. By yielding, the profession would possibly lose something of its self-respect, and it must be remembered that when a profession loses that, public respect may also be lost.

* * *

I well recall a visit to the office of a physician in the United States. A man brought in his diabetic child for a routine check, and looking up his case record, the physician commented that he was some weeks overdue with his appointment. The man explained that the child had been sick, for "the virus" had been going around their home. At the mention of the word virus, the physician leaned forward in his chair, turned to me and asked, "Do you have the virus in your country, doctor? We have it over here, but I have not found it yet."

The remark was said in jest, but, of course, it contained more than a grain of truth because in spite of all the active research in virology knowledge of the virus still remains incomplete.

Research at the Cavendish Laboratory in Cambridge recently reported in *Nature* has suggested that all small viruses may have the same basic structure, consisting of a core of ribonucleic acid surrounded by a large number of identical protein molecules. In rod-shaped viruses these protein units are probably arranged in a spiral around the core whereas in the spherical viruses the units are packed symmetrically around the core. Virus research certainly seems to be yielding information that may be as fundamental to biology as atomic research has been to physics. There seems no doubt that virus studies will make it easier to understand many kinds of biologic processes — so that the search for "the virus" must continue.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42221

PRESENTATION OF CASE

First admission. A sixty-three-year-old man was admitted to the hospital because of diplopia.

Two years before entry he noted fatigue, malaise, palpitation, intermittent polyuria, polydipsia and a weight loss of 35 pounds. Six months later there was an episode of dizziness on a hot day. Dyspnea, anorexia, weakness and pallor were noted. Examination of the blood was said to have revealed a macrocytic anemia. X-ray films of the chest and an upper gastrointestinal series were normal. After treatment with vitamin B_{12} and liver injections he felt better, and a month later the hemoglobin was normal. A year before admission there was a recurrence of previous symptoms, with frequent dizzy spells and weight loss. Four months later blurring of vision and intermittent weakness and paresthesias of the legs were noted. Four months before entry, because of weakness and drowsiness, cortisone was given, with dramatic improvement. A month before admission, after losing consciousness and striking his head, he noted persistent diplopia, with a constant dull ache behind the eyes, especially on the right. There was a sudden decrease in visual acuity, with photophobia. Streaks seemed to radiate from a single light source in the field of vision. Examination of the eyes showed ptosis of the left eyelid; the left pupil was larger than the right, but both pupils reacted to light; the ocular tension and the fundi were normal; diplopia, bilateral central scotomas and a lower-temporal-visual-field defect on the right were noted.

For several years before admission there had been increasing constipation. During the year before admission the patient's weight was less than 125 pounds. He had worked as a lead solderer for many years.

Physical examination revealed a chronically ill, confused, lethargic, sullen man. The skin was pale and doughy. Chest, axillary and pubic hair was sparse. Ophthalmologic examination showed paralysis of the third and fourth cranial nerves on the left. The left pupil was larger than the right and reacted poorly to light. Diplopia, bitemporal hemianopsia and bilateral central scotomas were noted. There was some pallor of the optic disk on the left. Examination of the lungs showed hyperresonance and diminished breath sounds. The heart and abdomen were normal. The testes were atrophic. Neurologic examination revealed diminished vibration and position sense of the legs, especially on the left. A plantar extensor reflex was elicited bilaterally.

The temperature was 101.2°F., the pulse 78, and the respirations 14. The blood pressure was 98 systolic, 68 diastolic.

The urine was normal, with a specific gravity of 1.001. The minimum excretion of sodium in the urine was 20 milliequiv., and the maximum more than 700 milliequiv. per twenty-four hours. The urinary 17-ketosteroid excretion was 0.9 mg. per twenty-four hours. Examination of the blood revealed a hematocrit of 53.5 per cent and a white-cell count of 12,200, with 66 per cent neutrophils. The eosinophil count was 55. The nonprotein nitrogen was 21 mg., the calcium 8 mg., the phosphorus 4.3 mg., the total protein 7.2 gm., the iron 110 microgm., and the fasting blood glucose 96 mg. per 100 ml. The sodium was 137 milliequiv., the potassium 3.5 milliequiv., the chloride 103 milliequiv., the carbon dioxide 24 milliequiv., and the total solutes 277 milliosmols per liter. The basal metabolic rate was −11 per cent. The uptake of radioactive iodine was 1 per cent in twenty-four hours. The serum protein-bound iodine was 1.6 gamma per 100 ml. Blood cultures were negative. A throat culture grew out a few alpha-hemolytic streptococci. X-ray films of the chest showed some flattening of the diaphragm and a moderate increase in the pulmonary markings; the heart and mediastinum were normal. Skull films demonstrated decalcification of the dorsum sellae turcicae. An electrocardiogram showed a normal sinus rhythm at a rate of 80, with occasional premature ventricular beats; the mean QRS vector was +90°; the PR and QRS intervals were 0.18 and 0.08 second, respectively; the T waves were inverted in Leads 3, aVF and V_1 through V_5; there was borderline low voltage. A lumbar puncture yielded 6 ml. of clear acellular cerebrospinal fluid under an initial pressure equivalent to 50 mm. and a final pressure equivalent to 0 mm. of water; the protein was 134 mg. per 100 ml., and the gold-sol curve 1122321000; a Hinton test was negative.

The hospital course was characterized by episodes of fever, hypotension, drowsiness or manic excitement and marked instability of water and electrolyte concentrations. Because of mild hypotension, disorientation and dehydration during the first week the patient was given fluids intravenously and hydro-

cortisone, 25 to 100 mg. daily, with improvement. The daily water turnover was more than 4 liters. With Pitressin the output of urine fell to less than 1 liter per day. In preparation for a pneumoencephalogram on the sixth hospital day he was given 8 mg. of morphine and strapped in the sitting position for five minutes. The blood pressure and pulse became unobtainable, and he lost consciousness. Placing him in a supine position failed to raise the blood pressure. Nor-epinephrine given intravenously was required for five days to maintain the blood pressure above 100 systolic. Thyroid administration was begun. On the seventh hospital day intestinal ileus occurred and lasted for several days, during which the patient was in a state of agitated confusion progressing to coma. On the tenth hospital day the serum sodium was 117 milliequiv., the potassium 3.8 milliequiv., the chloride 83 milliequiv., and the carbon dioxide 23 milliequiv. per liter. The urinary sodium was 248 milliequiv., and the chloride 289 milliequiv. per twenty-four hours. Coincidental with a marked diuresis and with intubation and intravenous hydrocortisone therapy the abdominal distention subsided, and the mental status improved. On the twelfth hospital day the serum sodium was 130 milliequiv., the potassium 3.9 milliequiv., the chloride 96 milliequiv., and the carbon dioxide 23 milliequiv. per liter. The serum total protein was 4.6 gm., the albumin 3.2 gm., the globulin 1.4 gm., the calcium 6.8 mg., the phosphorus 2.4 mg., and the fasting blood glucose 100 mg. per 100 ml. At this time the temperature rose to 103.6°F., but subsequently fell to normal. A blood culture showed no growth. Intravenous administration of nor-epinephrine was necessary for maintenance of the blood pressure at normal levels. During the next four days the serum sodium ranged between 114 and 129 milliequiv., the potassium between 2.5 and 3.7 milliequiv., the chloride between 76 and 96 milliequiv., the carbon dioxide between 22 and 25 milliequiv., and the total solutes between 220 and 258 milliosmols per liter. The urinary sodium excretion ranged between 9 and 155 milliequiv., the chloride between 16 and 164 milliequiv., the potassium between 8 and 47 milliequiv., and the total solutes between 24 and 405 milliosmols per liter; the pH ranged between 6.5 and 7. Saline solution was given intravenously in amounts calculated to match the urinary sodium losses. There was a steady rise in urine output to a peak of 7500 ml. per day. With Pitressin the urine total solute concentration was 200 to 500 milliosmols per liter. The patient complained of hydrophobia. The body weight at this time was 143 pounds.

A second attempt to do a pneumoencephalogram on the twenty-third hospital day resulted in a transient syncopal attack. The serum sodium was 119 milliequiv., the potassium 3.1 milliequiv., the chloride 74 milliequiv., the carbon dioxide 31 milliequiv., and the total solutes 248 milliosmols per liter; the pH was 7.53. Three days later a pneumoencephalogram demonstrated dilatation of the lateral ventricles and the third ventricle; there appeared to be a mass occupying the region of the peduncular and chiasmatic regions and elevating the floor of the third ventricle.

Omission of intravenous infusions of fluids resulted in a sharp drop of water and sodium intake and a large negative water balance, with a weight loss of 20 pounds. The blood pressure ranged between 100 and 120 systolic while the patient remained in bed. The urinary sodium excretion diminished, and the serum sodium rose to normal. The twenty-four-hour turnover of water fell to as low as 1500 ml. On one occasion, because of dehydration, the serum sodium rose to 161 milliequiv. per liter. At this time the patient had no apparent sensation of thirst and was very drowsy. His weight remained fairly steady at 114 pounds. Subsequently, with a constant daily dose of Pitressin and varying of the water intake inversely with change in weight, the weight was maintained at about 107 pounds. On the thirty-fourth hospital day the total serum protein was 5.8 gm., the albumin 4.4 gm., and the globulin 1.4 gm. per 100 ml. The serum electrophoretic pattern was normal.

From the thirty-sixth to the fifty-seventh hospital day the suprasellar region was irradiated with 3000 r through opposing bilateral ports with a 2,000,000-volt machine. The palsies of the left third and fourth cranial nerves and ptosis disappeared. Visual acuity increased from 20/300 to 20/70 in both eyes, with disappearance of diplopia. The bitemporal hemianopsia persisted. The patient became more alert but continued to have episodes of drowsiness. When ambulatory he had occasional episodes of postural hypotension. Methyl testosterone was begun on the fifty-second hospital day. He was discharged on the seventy-fifth hospital day on cortisone, 20 mg., thyroid, methyl testosterone, sodium chloride and potassium chloride daily, and Pitressin every other day.

Final admission (ten weeks later). He remained well until four weeks before entry, when there was an episode of hypotension and hyponatremia. The blood glucose was normal. Two weeks later he became drowsy and febrile, with stiffness of the neck. A lumbar puncture yielded grossly bloody cerebrospinal fluid without xanthochromia; it contained 50 lymphocytes per cubic millimeter and 59 mg. per 100 ml. of protein; a culture was negative. Except for visual deterioration there was improvement after intravenously administered fluid and Achromycin therapy. Three days before admission he became weak and anorectic, with ataxia and progressive diminution of vision to 20/200 in both eyes. Bilateral optic atrophy was noted.

Physical examination showed impairment of recent memory, unsteadiness of gait, photophobia, im-

pairment of upward gaze, a marked decrease in visual acuity and bitemporal hemianopsia. The pupils reacted normally. Plantar responses were questionably extensor. The weight was 101 pounds.

The temperature was 98°F., the pulse 88, and the respirations 18. The blood pressure was 118 systolic, 76 diastolic.

The urine was normal; the urinary sodium was 110 milliequiv., the chloride 129 milliequiv., and the total solutes 465 milliosmols per liter. Examination of the blood revealed a hemoglobin of 15.5 gm. per 100 ml., with a hematocrit of 51 per cent and a white-cell count of 7700. The nonprotein nitrogen was 22 mg., the total protein 6.4 gm., the uric acid 10.8 mg., and the fasting blood glucose 75 mg. per 100 ml.; the serum sodium was 138 milliequiv., the potassium 5.3 milliequiv., the chloride 105 milliequiv., and the carbon dioxide 28 milliequiv. per liter. The serum pH was 7.47. An electroencephalogram showed activity slower than normal, without localization. An electrocardiogram was normal except for a QT interval of 0.40 second (normal, 0.37 second). X-ray

FIGURE 1. *Anteroposterior Film of the Skull, Showing Destruction of the Right Lesser Sphenoid Wing (Arrows).*

films of the skull showed marked thinning of the posterior clinoid processes and considerable decalcification of the dorsum sellae turcicae, with destruction of the lesser sphenoid wing on the right (Fig. 1 and 2); there was calcification of the choroid plexuses and of the internal carotid vessels as they overshadowed the pituitary fossa.

There continued to be marked postural hypotension. The temperature ranged between 96 and 102°F. On the eighth hospital day, when the serum sodium was 162 milliequiv. per liter, the patient did not complain of thirst. The serum sodium ranged between 130 and 165 milliequiv., the potassium between 3 and 5.1 milliequiv., the chloride between 86 and 124 milliequiv., and the carbon dioxide between 20 and 27 milliequiv. per liter, and the serum nonprotein nitrogen between 27 and 42 mg. per 100 ml. The urinary sodium ranged between 3 and 98 milliequiv., and the potassium between 2 and 135 milliequiv. per liter. On the thirteenth hospital day there was a dramatic depression in the state of consciousness, deepening to coma with fixed dilated pupils and a divergent strabismus. The blood pressure was unobtainable. The serum electrolytes and the body weight showed no significant change. With intravenous administration of nor-epinephrine and hydrocortisone,

FIGURE 2. *Lateral View of the Skull, Showing Thinning of the Dorsum Sellae Turcicae (Arrows).*

together with sympathomimetic amines given intramuscularly, the blood pressure was restored. The patient responded to painful stimuli and made monosyllabic responses but did not regain adequate contact with the environment. After twelve days on pressor amines given intravenously the respirations suddenly became irregular, and he died on the twenty-fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. PHILIP H. HENNEMAN*: This sixty-three-year-old man had a neurologic problem, an endocrinologic problem and a profound and unusual disturbance in salt and water metabolism. Before discussing the case in detail I should like to comment on the anatomy of the area involved and on five of the factors that control salt and water metabolism.

The third ventricle[1] is connected to the lateral ventricles by the foramens of Monro and to the fourth ventricle via the aqueduct. The floor of the third ventricle is formed by the hypothalamus, suspended from which is the pituitary body. There are collections of nuclei in the anterior hypothalamus whose long axons pass through the hypothalamus and the pituitary stalk to terminate in the posterior pituitary lobe. It is now believed that antidiuretic hormone

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is formed by these cells in the anterior hypothalamus and is transported down these long axons as visible neurosecretory granules[2] to be stored in and secreted from the posterior pituitary lobe.

The next digression concerns five of the mechanisms of controlling salt and water metabolism in the body: thirst, salt appetite, hydrocortisone secretion by the adrenal cortex, antidiuretic-hormone secretion by the posterior pituitary lobe and aldosterone secretion by the adrenal cortex. The first of these, thirst, is perhaps the least well understood. There appears to be a center in the hypothalamus that is able to measure either the osmolarity of the blood or the concentration of intracellular water. If such a center exists, fibers must pass from it to the cerebral cortex since thirst is a conscious sensation. Furthermore, this center is able to recognize excessively high concentrations of water as an abhorrence of water or hydrophobia. Normally, the sense of thirst accurately adjusts the voluntary water intake to meet the necessary water loss of perspiration, insensible loss through the lungs and water loss in the urine and feces. Any interference with the pathway between the hypothalamus and the cerebral cortex obviously can interfere with a normal thirst.

A salt appetite can be clearly demonstrated in certain animals. Rats depleted of salt will select from several drinking sources the one that will supply an adequate amount of salt to restore the salt balance to normal. Human beings are unique animals in that they normally live on a high-salt intake. I have not been impressed with the capacity of patients to identify their specific need for salt.

Hydrocortisone secretion by the adrenal cortex is an important factor in control of salt and water metabolism. Patients with primary or secondary adrenal insufficiency are relatively unable to conserve water and to excrete rapidly a water load. This forms the primary basis for the water-tolerance test.[3] The patient with Addison's disease has a decreased rate of water absorption from the intestines. This does not wholly explain the water intolerance since a normal rate of water absorption can be restored by a high-salt intake or desoxycorticosterone acetate, but these measures do not restore normal water tolerance. Hydrocortisone administration restores water tolerance within two or three hours of its administration. Leaf et al.[4] demonstrated that hydrocortisone does not block the peripheral effect of antidiuretic hormone. Hydrocortisone does increase the glomerular filtration rate; this probably has a profound effect on the ability rapidly to excrete a water load. On the other hand, a high-salt intake and desoxycorticosterone acetate will raise the glomerular filtration rate of the patient with Addison's disease to nearly normal, but they do not correct the specific defect in the handling of water. There remains a possible direct action of hydrocortisone on the renal tubular handling of water. The rate of hydrocortisone secretion is determined by ACTH secretion of the anterior lobe of the pituitary body; the main stimuli to ACTH secretion appear to be low blood levels of hydrocortisone and epinephrine and the stimulation of the central nervous system by stress.

The secretion of antidiuretic hormone by the posterior pituitary body increases tubular reabsorption of water in the kidney. The stimulus to increased antidiuretic-hormone secretion appears to be hyperosmolarity of the serum and extracellular fluid. One center for recognition of hyperosmolarity is in the anterior hypothalamus and seems to be separate from the center for thirst in that most patients with diabetes insipidus have an intact sense of thirst and are able to meet their obligatory large water losses by a large water intake.

A fifth factor in salt and water metabolism is aldosterone — the newest adrenal hormone isolated and identified. The administration of minute amounts, 25 to 50 microgm. a day, causes retention of sodium and excretion of potassium. Aldosterone secretion apparently is not under the control of the anterior pituitary lobe as the other adrenocortical hormones are. The "control center" is unknown at the present time. In general, circumstances that elicit increased aldosterone secretion are those in which extracellular fluid volume is decreased. Perhaps there are centers in the great vessels of the chest that are able to measure extracellular volume and communicate this information to the adrenal cortex. Patients with hypopituitarism have an almost intact aldosterone secretion. Aldosterone assays are not generally available at the present time; the urinary sodium excretion under most circumstances is an inverse reflection of the level of aldosterone secretion.

A point first brought to my attention by Dr. Elbert P. Tuttle, Jr., is that the responses of antidiuretic hormone and aldosterone secretion are usually in the direction of restoring a normal extracellular fluid volume and not necessarily in the direction of restoring a normal serum sodium. An example of this rule, as demonstrated by Leaf and others,[5] is that water intoxication (induced by Pitressin together with a large water intake) is followed by a large urinary sodium excretion and a further fall in serum sodium, apparently as a consequence of decreased aldosterone secretion. Marked thirsting with dehydration and fall in extracellular fluid volume not only stimulates release of antidiuretic hormone but also secondarily stimulates secretion of aldosterone, so that the urinary sodium excretion falls and sodium is retained.

Let us now turn to the case history. Because of the length and complexity of the case, I shall take it up in three parts: the general medical and neurologic findings; the evidence for anterior and posterior pituitary insufficiency; and, finally, the marked changes in salt and water balance. This patient's illness ap-

parently began two years before entry; he died about four months after the first admission; therefore, the total duration of the illness was two years and four months. The first symptoms were polyuria, polydipsia and certain other nonspecific complaints. Polyuria and polydipsia should make the physician think of diabetes insipidus, diabetes mellitus, hypercalcemia and kidney disease. Subsequently, there was decreased visual acuity, and on examination there were signs compatible with left-third-nerve paralysis — namely, ptosis, an enlarged left pupil and diplopia. The first examiner noted a lower-temporal-visual-field defect.

On initial physical examination the patient appeared chronically ill, with signs of interference of cerebral function in the form of confusion, lethargy and dullness, of paralysis of the third and fourth nerves on the left, and of bitemporal hemianopsia. This evidence places a lesion in the region of the optic chiasm and in the region of the passage of the third and fourth nerves from the nuclei in the midbrain anteriorly to the globe. The blood pressure was rather low, 98 systolic, 68 diastolic. The x-ray examination demonstrated decalcification of the dorsum sellae turcicae. Somewhat later the first indication of postural hypotension appeared. When the patient was strapped in a chair for a pneumoencephalogram he collapsed and had a low blood pressure. Repeatedly throughout the history mention is made of postural hypotension. This was probably caused in part by the secondary adrenal insufficiency. However, most episodes of hypotension were clearly related to posture and were reminiscent of the postural hypotension seen in patients after extensive bilateral thoracolumbar sympathectomy. In view of the evidence for involvement in the area of the hypothalamus one thinks of damage to centers that play upon medullary control of pulse rate and blood pressure. The hypothalamus is not the prime center for the control of pulse and blood pressure, since an animal from whom the hypothalamus has been removed has a normal pulse and blood pressure. Nevertheless, it can be demonstrated that the hypothalamus sends impulses to the medulla and can markedly alter pulse and blood pressure. White[6] reported a series of experiments in which he stimulated the hypothalamus in patients under local anesthesia. Stimulation of the anterior hypothalamus produced tachycardia, and a rise in blood pressure; stimulation somewhat posteriorly resulted in bradycardia and a fall in blood pressure. It would be of interest to know whether or not this patient had bradycardia at the same time that he had these marked falls in blood pressure. Is that information readily available?

Dr. Elbert P. Tuttle, Jr.: I think that on at least one occasion he had bradycardia and also sweating; he had a vasovagal picture at the time of syncope on one occasion.

Dr. Henneman: Dr. White also pointed out that ether and atropine prevented the response of the blood pressure to hypothalamic stimulation. Atropine blocks the release of acetylcholine by the vagus nerve and thus prevents cardiac slowing. Brewster, Bunker and Beecher[7] have indicated that ether causes the release of epinephrine and probably nor-epinephrine from the adrenal medulla. Perhaps for this reason ether masks some of the cardiovascular effects of stimulation of the hypothalamus. Interestingly enough the patient under discussion responded well to nor-epinephrine given intravenously; on numerous occasions this seemed to be the only means by which the blood pressure could be maintained within reasonable limits. A prolonged requirement for nor-epinephrine would be compatible with interference with the sympathetic and parasympathetic control of blood pressure.

The third attempt to do a pneumoencephalogram in this patient demonstrated dilatation of the lateral and third ventricles. There appeared to be a mass occupying the peduncular and chiasmatic regions and elevating the floor of the third ventricle. A mass in this region might block the flow of cerebrospinal fluid and cause dilatation of the third and fourth ventricles without a rise in spinal-fluid pressure.

From the thirty-sixth to the fifty-seventh hospital day, the patient received radiation therapy, after which the palsy of the third and fourth nerves and the ptosis disappeared and visual acuity improved. Whatever the lesion in this region was, it apparently was quite radiosensitive. Dr. Albright has indicated that the maximum response of pituitary tumors to irradiation is achieved in about four months. It is of interest that thirteen weeks after the beginning of x-ray therapy this patient suddenly became worse; he became drowsy and febrile, with stiffness of the neck and deterioration of vision, perhaps reflecting necrosis and hemorrhage of a radiosensitive tumor.

Physical examination at this time revealed a new sign — namely, impairment of upward gaze. This, I believe, is a specific neurologic finding related to pressure on the superior colliculus. Impairment of upward gaze is a typical finding in patients with a pinealoma with pressure on the superior colliculus. X-ray films at this time demonstrated marked thinning of the posterior clinoid processes and of the lesser sphenoid wing on the right. May I see the x-ray films?

Dr. Richard V. Wilson: The pneumoencephalogram was borrowed and was not returned. The only films that we have are those taken after the pneumoencephalogram. The film of the skull shows virtual destruction of the right lesser wing of the sphenoid (Fig. 1).

Dr. Henneman: Is the destruction near nerve foramens?

Dr. Wilson: No.

DR. HENNEMAN: Is the bone destruction nearly 3 cm. from the mid-line?

DR. WILSON: The destruction starts about 2 cm. from the mid-line, and there seems to be almost no bone lateral to this point. The posterior clinoid processes are thin shells of bone. When I looked at the films with the stereoscope, both the anterior and the posterior clinoid processes were more eroded on the right side than on the left. The anterior clinoid processes are poorly seen because they are quite pointed.

DR. HENNEMAN: Is the sella turcica ballooned?

DR. WILSON: The sella turcica looks slightly enlarged.

DR. HENNEMAN: Is it large by measurement?

DR. WILSON: I did not measure it. None of these are completely true lateral views. I, myself, should say from the size of the sella turcica that the primary process was not intrasellar, but probably above the sella. The tiny calcifications on the stereoscopic examination appeared to be in the internal carotid arteries. The sphenoid sinus appears normal although the posterior wall of the sphenoid sinuses looks fuzzy. The examination of the chest is negative for a man of this age.

DR. HENNEMAN: Can you see any evidence of hyperostosis around the sella turcica?

DR. WILSON: No; I do not see any bone production.

DR. HENNEMAN: Can you see notching of the clivus such as one would find with a chordoma?

DR. WILSON: No; certainly, this is not the x-ray appearance of a chordoma.

DR. HENNEMAN: You do not see any evidence of a primary tumor in the lung?

DR. WILSON: No.

DR. HENNEMAN: Thereafter, hypotension and a profound depression of the state of consciousness developed, progressing to coma. The patient died in spite of restoration of the blood pressure to normal by sympathomimetic amines.

Thus, the clinical course, which covered two years and four months, was characterized by evidence of a lesion anterior to the sella turcica on both the right and left sides, impinging on the optic chiasm, elevating the floor of the third ventricle, producing pressure on the superior colliculus and blocking outflow of fluid from the third and lateral ventricles. Apparently, the process was diffuse, was radiosensitive and underwent necrosis, perhaps as a late consequence of the x-ray treatment.

The initial evidence for anterior pituitary insufficiency is the fatigue, malaise and weight loss — all nonspecific symptoms. With equal depression of all pituitary hormones the resulting symptoms tend to be much less marked than with depression of a single hormone such as occurs in primary myxedema or primary adrenal insufficiency. Note is made of a macrocytic anemia that seemed to respond to vitamin B_{12}. We have seen a number of patients with panhypopituitarism in our Endocrine and Ovarian Dysfunction clinics who have demonstrated an anemia that was usually macrocytic and might be associated with a megaloblastic bone marrow. This anemia has tended to have exacerbations and remissions; it has not become very severe, nor has it gone into complete remission. It has been our impression that testosterone and sometimes liver extract improved this anemia. With the advent of cortisone therapy, this type of anemia has disappeared. It seems clear that cortisone has a hematopoietic activity in patients with hypopituitarism, but the dynamics and the mechanics of this action have yet to be worked out. Thus, macrocytic anemia is at least compatible with the diagnosis of anterior pituitary insufficiency.

Somewhat later, the patient was given cortisone. I am afraid that at the present time almost anyone who is mortally ill, and for whom the physician can do nothing else, may receive cortisone. At any rate our present patient improved dramatically. Cortisone restores patients with anterior pituitary insufficiency to normal health and vigor. We have no laboratory test to measure this response; we must judge the adequacy of the cortisone dose on the basis of how the patient feels.

On physical examination initially the patient's skin was pale and gray and the hair on the body was sparse — findings that suggest a decrease in androgen secretion by the testis and adrenal gland. Indeed, on examination the testes were noted to be atrophic, and the 17-ketosteroid excretion was also extremely low. Additional evidences for pituitary insufficiency were the low basal metabolic rate, the low radioactive-iodine uptake and the low serum protein-bound iodine. The evidence for posterior pituitary insufficiency is not so definite. The patient had polyuria and a low urinary specific gravity. The diagnosis of diabetes insipidus is best made on the basis of hyperosmolarity of the serum associated with a dilute urine. These data are not presented. The changes in body weight and serum sodium are the best indicators of the profound alterations in salt and water metabolism that this patient demonstrated. At the time of admission the serum sodium was normal. Hypotension developed, and fluids were given intravenously along with nor-epinephrine. Nor-epinephrine cannot be given in a concentrated form; usually 4 mg. is diluted in a liter of 5 per cent glucose. If the patient required much nor-epinephrine, one can assume that he received large quantities of water intravenously. In the second week the serum sodium was 117 milliequiv. per liter. Previously, the ability to conserve sodium had been clearly demonstrated; he was able to limit the daily urinary sodium excretion

to 20 milliequiv. and to increase it to as much as 700 milliequiv. on demand. Shortly thereafter, he was given more nor-epinephrine, presumably in water, and the serum sodium fluctuated in the range of 120 milliequiv. per liter. Somewhat later, when fluids were withheld, the weight fell to 123 pounds, and the serum sodium rose to normal — indeed, to supernormal — levels, reaching 165 milliequiv. per liter on two occasions. At these times of hyperosmolarity of the serum he did not complain of thirst; this is evidence for lack of the thirst mechanism. Since he could conserve and excrete sodium and had diabetes insipidus, I assume that he lacked antidiuretic hormone but had normal control of aldosterone secretion. When the extracellular fluid volume was overexpanded by intravenous fluid therapy, aldosterone secretion secondarily decreased, resulting in large urinary sodium losses and a further fall in the serum sodium.

What are the possible lesions in the pituitary region that could produce this clinical picture? At the onset one should point out that diabetes insipidus is rare with any tumor in this region. The most common tumors in this area are craniopharyngioma and pituitary adenoma. Craniopharyngiomas arise from the remnant of squamous epithelium enclosed during infolding of the brain and of the pharynx during embryonic life and are composed of squamous epithelium, often with cholesterol crystals in the cystic spaces; occasionally, they behave like carcinomas. A pituitary adenoma, particularly a chromophobe adenoma, could also explain the pituitary insufficiency. It would be surprising for a large pituitary adenoma to be present without more expansion of the sella turcica than this patient showed. Among the less likely possibilities are chordomas, which occasionally arise at the junction of the sphenoid and occiput. There is apparently a specific x-ray sign associated with chordomas — a notching of the clivus. Chordomas arise from embryologic remnants of the notochord. Adenocarcinoma of the anterior pituitary body is another possibility. This tends to be a destructive, rapidly progressing lesion and, I believe, not infrequently undergoes spontaneous infarction — so-called pituitary apoplexy. Gliomas and meningiomas may arise in this region. Meningiomas may be associated with localized hyperostosis cranii.

At least 2 cases similar to this have been reported[3,8]; Dr. Albright's patient, described by Leaf, had the Hand–Schüller–Christian syndrome — that is, an eosinophilic granuloma destroying bone and producing anterior and posterior pituitary insufficiency. Eosinophilic granuloma is also transiently radiosensitive and deserves consideration. I know of no other way to add to or detract from that diagnosis.

There remains for consideration the pinealoma, which may invade the floor and the lateral wall of the third ventricle. Pinealoma is extremely rare in older persons and, indeed, is a very rare tumor to begin with. It is the only tumor of those that I have mentioned that is significantly radiosensitive. Therefore, I think that it deserves special consideration. Patients with pinealomas frequently have cells in the spinal fluid that look like lymphocytes. Terminally, the patient under discussion did have a considerable number of "lymphocytes" in the spinal fluid.

In spite of the features in favor of pinealoma I think that one should be conservative under such circumstances and choose the commonest tumor, a craniopharyngioma, which can produce insufficiency of the anterior and posterior pituitary body, destruction of the sella turcica, obstruction of the aqueduct and pressure on the second, third and fourth cranial nerves.

DR. JACOB LERMAN: I wonder whether a granulomatous lesion in that region would destroy the pituitary body by producing external pressure on it.

DR. RICHARD B. COHEN: Occasionally, a focal granulomatous lesion such as a gumma or tuberculoma in the region of the aqueduct may produce increased intracranial pressure.

DR. WILSON: I have never seen a craniopharyngioma destroy bone as far laterally as the lesser wing of the sphenoid process is destroyed here.

DR. HENNEMAN: What would your diagnosis be?

DR. WILSON: I should choose a more common type of brain tumor, beginning in the suprasellar area, either a glioma metastasis or any type of pituitary lesion.

DR. FARAHE MALOOF: I should think, from the observations that we have made in the past several years, that this uptake of radioactive iodine by the thyroid was really out of line with the other tests of thyroid function. The patient may have been receiving some medication that produced the low uptake, which suggests that he had no functioning thyroid tissue.

The uric acid level of 10.8 mg. per 100 ml. was high. I have seen a similar patient with a high serum uric acid level; he had arthritic symptoms suggestive of rheumatoid arthritis. I wonder if Dr. Henneman can explain the uric acid elevation in the serum of this patient.

DR. HENNEMAN: No.

DR. COHEN: Dr. Henneman, do you think that cortisone or thyroid therapy will cause an exacerbation of diabetes insipidus in patients who have destructive lesions of the pituitary gland with diabetes insipidus and who also have a decrease in thyrotropin and ACTH production?

DR. HENNEMAN: Yes; it may be difficult to maintain such patients on cortisone therapy.

DR. COHEN: The pituitary insufficiency in association with the adrenal and thyroid failure represents

a difficult problem, for when the thyroid or adrenal failure is treated specifically the severity of the diabetes insipidus may be increased.

DR. MALOOF: Regarding the hypotension after the ventriculogram, the administration of 8 mg. of morphine to this patient might have had something to do with it. There is certainly some risk in giving a patient with low thyroid function that much morphine.

DR. TUTTLE: I believe that morphine does have a very small effect on the blood pressure.

A PHYSICIAN: Has diabetes insipidus been the first sign of craniopharyngioma? I do not know why it should not be, but I cannot recall that it has been.

CLINICAL DIAGNOSES

Panhypopituitarism.
Neoplasm of pituitary, with suprasellar extension.

DR. PHILIP H. HENNEMAN'S DIAGNOSES

Craniopharyngioma.
Panhypopituitarism, with anterior and posterior pituitary insufficiency.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of left adrenal gland, with metastases to anterior and posterior pituitary, hypothalamus, liver, lung and retroperitoneal lymph nodes.

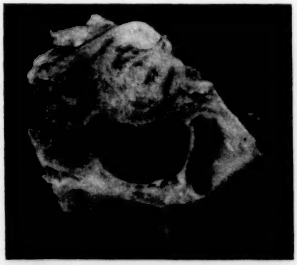

FIGURE 3. *Section through the Sella Turcica and Sphenoid, Showing Replacement of the Pituitary Body by Tumor and Extension of the Tumor beyond the Confines of the Sella.*

PATHOLOGICAL DISCUSSION

DR. COHEN: At autopsy the body was that of a well developed, fairly well nourished man with the waxy pallor occasionally observed in pituitary deficiency. The axillary hair was sparse to absent, and the pubic hair was scanty. The most significant changes were in the region of the pituitary. The gland was almost completely replaced by a grayish-yellow, partially necrotic tumor, which filled the sella and extended beyond it, encasing the pituitary stalk and involving the optic chiasm posteriorly and the oculomotor nerves bilaterally (Fig. 3). The tumor extended into the hypothalamus in the region of the supraoptic nuclei. Sections examined microscopically revealed it to be a poorly differentiated adenocarcinoma. The left adrenal gland was completely replaced by a large, gray-white tumor mass, quite distinct from the kidney (Fig. 4), that was histologically identical to the tumor in the brain and pituitary. Although not typical of adrenal carcinoma, it did resemble several adrenocortical carcinomas that we have seen whose primary cortical origin was supported by clinical manifestations of hyperadrenocorticism. A careful search for other tumor revealed metastases in retroperitoneal lymph nodes, an isolated focus in the liver and a microscopic collection of tumor cells in the lung. There were scattered metastases in the brain. It is unlikely that any of these represented primary sites.

FIGURE 4.

The testes were atrophic; the thyroid was small, and the remaining adrenal gland was not remarkable.

DR. HENNEMAN: Could this have been a primary pituitary carcinoma with metastases to the adrenal gland? Many malignant tumors do metastasize to the adrenal gland.

DR. COHEN: The tumor did not look like a primary pituitary carcinoma. Any pathologic process that destroys the posterior pituitary, its stalk and the hypothalamus may produce the syndrome of diabetes insipidus. Prominent among these lesions are neoplasms, granulomas and the reticuloendothelioses. Nongranulomatous inflammatory reaction may result in the disease; vascular disturbances and even trauma have been implicated as etiologies. A few cases have been described in which no disease could be found by the methods utilized despite the presence of clear-cut diabetes insipidus during life. Spontaneous remissions

of frank cases have been reported. The syndrome of diabetes insipidus, however, is rare, probably because in general it is necessary that destruction be remarkably complete before the syndrome will ensue. It has been shown experimentally that at least 85 per cent of the cells in the supraoptic nuclei may be destroyed before diabetes insipidus will occur.

A new opportunity for the pathologist and histologist to contribute to the knowledge of the pathologic and physiologic mechanisms of the hypothalamohypophyseal system was provided by the discovery of evidence for neurosecretion[9] and the histochemical technics for staining these secretions.[10] With these technics considerable important information has already accrued,[2,11,12] and more is sure to appear.

DR. BENJAMIN CASTLEMAN: I think it might be mentioned that the relative rapidity of the course was the factor that made Dr. Roger Melick suggest a metastatic carcinoma. He had never seen a glioma or any of the other tumors mentioned above progress so rapidly.

DR. HENNEMAN: A twenty-eight-month course is unusually long for metastatic carcinoma in the brain. Perhaps metastasis of the adrenal carcinoma to the pituitary "hypophysectomized" the patient, retarding the growth of the tumor!

REFERENCES

1. Strong, O. S., and Elwyn, A. *Human Neuroanatomy.* 442 pp. Baltimore: Williams & Wilkins, 1943. P. 277.
2. Scharrer, E., and Scharrer, B. Hormones produced by neurosecretory cells. *Recent Progr. in Hormone Res.* **10**:183-240, 1954.
3. Robinson, F. J., Power, H. N., and Kepler, E. J. Two new procedures to assist in recognition and exclusion of Addison's disease: preliminary report. *Proc. Staff Meet., Mayo Clin.* **16**:577-583, 1941.
4. Leaf, A., Mamby, A. R., Rasmussen, H., and Marasco, J. P. Some hormonal aspects of water excretion in man. *J. Clin. Investigation* **31**:914-927, 1952.
5. Leaf, A., Bartter, F. C., Santos, R. F., and Wrong, O. Evidence in man that urinary electrolyte loss induced by Pitressin is function of water retention. *J. Clin. Investigation* **32**:868, 1953.
6. White, J. C. Autonomic discharge from stimulation of hypothalamus in man. *A. Research Nerv. & Ment. Dis., Proc.* (1939) **20**:854-863, 1940.
7. Brewster, W. R., Jr., Bunker, J. P., and Beecher, H. K. Metabolic effects of anesthesia. VI. Mechanism of metabolic acidosis and hyperglycemia during ether anesthesia in dog. *Am. J. Physiol.* **171**:37-47, 1952.
8. Engstrom, W. W., and Liebman, A. Chronic hyperosmolarity of body fluids with cerebral lesion causing diabetes insipidus and anterior pituitary insufficiency. *Am. J. Med.* **15**:180-186, 1953.
9. Scharrer, E., and Goupp, R. Neuere Befunde am Nucleus supraopticus und Nucleus paraventricularis des Menschen. *Ztschr. f. d. ges. Neurol. u. Psychiat.* **148**:766-772, 1933.
10. Gomori, G. Observations with differentiated stains on human islets of Langerhans. *Am. J. Path.* **17**:395-406, 1941.
11. Bodian, D. Nerve endings, neurosecretory substance and lobular organization of neurohypophysis. *Bull. Johns Hopkins Hosp.* **89**:354-376, 1951.
12. Smith, S. W. Correspondence between hypothalamic neurosecretory material and neurohypophyseal material in vertebrates. *Am. J. Anat.* **89**:195-232, 1951.

Correction. In the paper entitled "Frequency of the Asymptomatic Lower Esophageal Contractile Ring," by Dr. Philip Kramer, which appeared in the April 12 issue of the *Journal,* the last sentence of the legend for Figure 1 should be changed to read: "After a bread-barium swallow (not shown here), he complained of dysphagia, and the bread could be seen obstructing the residual esophageal lumen."

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THE EPIDEMIOLOGIC METHOD

THE last ten years have seen a growing appreciation of the value of applying epidemiologic methods to the unknowns in noninfectious disease. The value of such an approach has in fact long since passed the theoretical stage, and the *Journal* reviewed two years ago the fruitful epidemiologic studies of angina pectoris and coronary-artery disease in bus drivers and conductors made by Morris and his colleagues.[1]

The historic use of the method was, of course, in the clarification of communicable disease; nor is there any sign that epidemiologic methods have lost any of their vitality when applied to the newest problem in immunity and contagion, — that of establishing present-day distributions of poliomyelitis, — and hence the efficacy of the vaccine. Knowledge of infectious processes advanced swiftly with the impetus given by the classic bacteriologic studies of Koch, Pasteur and many others. Consequently, the concern of older writers like Hirsch with the epidemiology of noninfectious (as well as infectious) diseases (such as goiter and plumbism) was relegated to a minor position for some fifty years while the study of microbiology and infection received major attention. One by one the great plagues were brought under control by the new sciences of bacteriology and immunology, and most physicians have never even been aware of the fact that there is an epidemiology of noninfectious heart disease, of goiter and of lead poisoning.

To study the importance of the injurious agent — whether it is living and therefore falling within the province of microbiology or inert and primarily of toxicologic interest — is but one step in orderly scientific procedure. Epidemiologic steps are to analyze constitutional and cultural attributes of those stricken by the disease — their age, sex, occupation or personal habits — that seem to provide an explanation for occurrence of the disease being studied. For example, the seasonal distribution of lead poisoning demonstrates the almost epidemic occurrence of clinical manifestations among children during the summer months. Although they may have been drinking lead-contaminated water or nibbling paint all winter, clearly a seasonal factor is involved. The number of cigarettes smoked or the age of one's mother may have nothing to do with the spread of poliomyelitis; they may have quite a little to do with lung cancer or certain of the congenital malformations. The modern attack on the latter problem may be said to have had its inception in 1940-41, when it was discovered that the prevalent congenital cataract had its genesis for the most part in German measles of the mother in the first trimester of pregnancy when the eyes of her baby were forming. This is of epidemiologic concern.

The origin of defects dating from birth involves a field about which ignorance is so complete that any contribution, whether it is of a clinical, laboratory or epidemiologic nature, is for the time being of special

research value; exceptions are the control of defects due to certain infections, notably syphilis and rubella. Mongolism, for example, illustrates how a relative control must await an improved knowledge of causation, and yet there are already a few tantalizing clues. Probably the most striking epidemiologic fact unearthed about any of the congenital defects is the relation of mongolism to advanced maternal age; the observation has been long established. The risk of producing a mongoloid child increases about fiftyfold, from around 0.3 per 1000 pregnancies at twenty to thirty years of age to around 15 in the fifth decade.

A beginning control of this lifelong defect of the central nervous system is to be expected only when the epidemiologic facts can be interpreted, expanded and given meaning. What are the factors associated with aging of mothers that combine to blight the differentiating brain, heart, eyes and little finger? Are they endocrine, gynecologic, systemic or combined? The answer to such questions, which are biologic, not statistical, are the crux of the problem of control. Geographic studies of mongolism have never been done on anything more than a tentative and inadequate basis, nor have secular occurrences or changes in maternal age distribution in different countries and at differing times been plotted, partly because mongolism occurs so rarely and partly because epidemiologic methodology has barely begun to be applied to congenital defects.

In its application to this and other noncommunicable diseases such as sarcoidosis, home accidents among the elderly, poisoning in infancy, and cancer, modern epidemiology is revealed as a method of study rather than a body of knowledge restricted to epidemics. It is the diagnostic discipline of public health even as physical diagnosis is a diagnostic discipline of clinical medicine, and it is a research tool by which to gain the knowledge of causation that is, in turn, usually essential to prevention.

Perhaps one of the most unusual applications of the epidemiologic method was the recent analysis of MacKinnon and MacKinnon[2] showing that suicides, fatal accidents and deaths from disease among women are far commoner in the follicular phase of the menstrual cycle than during other phases. This was the meaning of their provocative title: "Hazards of the Menstrual Cycle" and their suggestion that "highly strung women and those suffering from chronic disease should be warned of the hazards . . ."

No medical effort can effectively prevent or control disease — whether infectious or noninfectious, acute or chronic — if it does not take into account when and how those diseases are occurring in the community. The basic challenge today is to assemble the vital bits of knowledge that permit the metabolic diseases to be avoided rather than cured. Scurvy, pellagra, goiter and rickets are surely as open to control or at least as conquerable as yellow fever and whooping cough. The list is long and it is growing, but quite as long and impressive is the list of unknowns — atherosclerosis, peptic ulcer, diabetes, gout, cancer, arthritis and all the others that beckon the interested investigator.

References

1. Editorial. Busman's holiday. *New Eng. J. Med.* **250**:581, 1954.
2. MacKinnon, P. C. B., and MacKinnon, I. L. Hazards of menstrual cycle. *Brit. M. J.* **1**:555, 1956.

THE DISPENSING AND SALE OF DRUGS BY PHYSICIANS

During the current session of the Massachusetts State Legislature, an attempt has been made to eliminate the confusion regarding the interpretation of certain clauses of the law regulating the dispensing and sale of harmful drugs that was enacted in 1954. The matter has previously been discussed in these columns.[1,2] At its October meeting, the Council of the Massachusetts Medical Society passed a resolution that steps be taken "to encourage such legislative changes as may be necessary to make clear the right of a physician legally to administer and supply any drug at such time and under such circumstances as he in good faith and in the legitimate practice of medicine believes to be necessary for the alleviation of pain and suffering or for the treatment, alleviation or prevention of disease." After prolonged negotiations, amendments of the 1954 law have now been passed by the legislature. Although these do not employ the wording favored by the Society, it is hoped that any physician who supplies his patients with medicines in an ethical and proper manner can now feel free from fear that he may be penalized by a fine of $1,000 and a prison sentence of a year.

A clear understanding of the nature of the problems involved in this legislation requires a review of the circumstances relating to the enactment of the law (Chapter 577 of the *General Laws* of 1954) and the differences in the points of view concerning its interpretations that subsequently developed. The purpose of the new legislation was to bring the State regulations concerning the sale of harmful drugs into conformity with the federal law and also to introduce safeguards that might prevent abuses in the dispensing of barbiturates and amphetamines. A "harmful" drug by legal definition is any drug for which a prescription is required; in addition to barbiturates and amphetamines, this designation is applied to almost all drugs with active pharmacologic effects, including digitalis, sulfonamides and antibiotics. After the law had been enacted, representatives of the pharmaceutical profession claimed that it had now become illegal for a doctor to supply his patients with medicines in this class. It was claimed further that in this respect the new law superseded the existing law requiring

the registration of pharmacists, which specifically exempts "physicians who put up their own prescriptions or dispense medicines to their patients" (Section 35, Chapter 112, *General Laws of Massachusetts*).

The contention of the pharmacists was based on a section of Chapter 574, which states, "No person shall dispense any drug upon an oral or written prescription in a container which does not bear a label which gives the name and address of the druggist . . ." Another section of the law states, "No person shall sell or offer for sale at retail or dispense or give away any harmful drug to any person other than a physician, dentist or veterinarian, except upon oral or written prescription . . ." It was thus claimed that patients could legally obtain drugs only through the medium of a drugstore.

The problem became acute because of action taken by the House of Delegates of the American Medical Association at its meeting in June, 1955, which revised the wording of the *Code of Ethics* concerning the ownership of drugstores and dispensing of drugs and appliances by physicians. This section (Section 8 of Chapter 1, introduced in 1954) was deleted, and the following was substituted: "It is not unethical for a physician to prescribe or supply drugs, remedies, or appliances as long as there is no exploitation of the patient." The Massachusetts State Pharmaceutical Association immediately adopted a resolution that deplored and condemned this action of the American Medical Association. It urged the Association to rescind this amendment and also urged the Massachusetts Medical Society to indicate its disapproval.

The matter was considered by the Council of the Society in October. The Council not only endorsed the action of the American Medical Association but went further in adopting the recommendation quoted above. It was considered important to urge an immediate change in the law in view of the penalties provided for violation, including a fine up to $1,000 or imprisonment up to a year, or both.

The recent action by the legislature involves two slight changes. In the first place the word "harmful" was introduced to show clearly that the regulations refer only to harmful drugs. Secondly, the paragraph stating that "No person shall sell or offer for sale at retail or dispense or give away any harmful drug . . ." was modified by the insertion of the following sentence: "Nothing in this paragraph shall be construed to be in conflict with the provisions of paragraph 6 of this section." (Paragraph 6 reads as follows: "A physician, dentist or veterinarian may personally administer any harmful drug at such a time and under such circumstances as he in good faith and in the legitimate practice of medicine believes to be necessary for the alleviation of pain and suffering or for the treatment or alleviation of disease.")

This last section is believed to give legal approval to any proper and ethical sale of drugs by physicians provided a broad definition of the word "administer" is accepted. To administer can mean to give, supply and direct the application of a remedy. In the narrow sense, it might be contended that there is a violation of the law if the medicine is not actually received by the patient from the hands of the physician. Thus, a nurse giving a harmful drug might violate the law. This is one point that still needs clarification.

The wording of section 6 was taken from the Massachusetts law regulating the sale of narcotic drugs. It is therefore not a new restriction. Nurses and doctors probably can continue to carry on their work as usual without fear that they are in violation of the law. However, those who wish to have their rights and responsibilities clearly defined may perhaps seek to have a more exact definition of the meaning of "personal administration."

References

1. Editorial. October meeting of Council. *New Eng. J. Med.* **253**:741, 1955.
2. Editorial. Physician and pharmacist. *New Eng. J. Med.* **254**:289, 1956.

ECONOMIC FACTORS IN BLUE CROSS

In his 1955 report on Blue Cross, Mr. Roger W. Hardy, executive director of Massachusetts Hospital Service, Incorporated, revealed an increase in enrollment during that year of 144,225, bringing the total enrollment, as of January 1, 1956, to 2,269,505. Since some 3,500,000 Massachusetts residents have protection against hospital bills, through one agency or another, it is apparent that the large majority favor Blue Cross coverage. During the same year, according to the report, Massachusetts Blue Cross received $42,583,911 from subscribers, paid $39,495,469 for benefits, used 4.5 per cent of the subscriber's dollar for operating expenses and, including investment income, added $1,291,306 to principal. Reserves on December 31, 1955, for other than incurred obligations were $18,213,020.

Payments made to hospitals during the year were for 379,189 cases totaling 2,537,060 days; the average per diem payment to hospitals for special services increased from $6.10 on January 1, 1955, to $7.15 a year later. Other achievements listed include the 95 per cent coverage of the employees of the Commonwealth on a contributory basis, effective on January 1, 1956. Massachusetts is the first state to effect such a program.

Policies for prolonged-illness-certificate coverage increased from 75,000 to 231,000. Because of the potential financial hazard of selection, prolonged-illness coverage is available only to well employed groups that have both Blue Cross and Blue Shield. "However," the report states, "we know the necessity for reducing eligibility requirements for the Prolonged Illness Certificate when it can be safely done."

Not surprising is the contemplated increase of 2 per cent per year in rates because of the rise in number of days of hospitalization per 1000 member years and changing "economic factors and medical practices." This trend, according to the report, will require a 10 per cent increase in subscription charges over each five-year period. The "economic factors" as they affect Blue Cross are obvious. The $12 plan covered 81 per cent in 1953 and 77 per cent in 1955, and in 1956 it is expected to cover less than 75 per cent of the average bill.

That an increase in rates, however obvious, is somewhat hard to take, is recognized by Mr. Hardy, who writes: "In order to cover the same proportion of the average hospital bill as in the past, we soon will need a $15 plan for most of our members. Said in another way, our members will need a more expensive plan to provide the former service and we must persuade them of this need."

Another fact stressed in the report is as follows:

> . . . continuing increase in hospital costs at a greater rate than the average of all costs of living is inherent in the hospital function. Blue Cross and insurance companies must therefore increase their coverage for their members and enlarge membership because in no other way can hospitals obtain the money to accomplish their function.

In discussing coverage of municipal employees, Mr. Hardy points out that municipal officials want no part of a compulsory program. He adds:

> . . . but we cannot and no one can provide the same program at the same cost for 25 towns with 200 employees as we can give for one unit of 5,000 employees. Gross rates, net rates, the application of experience do differ on social and elementary actuarial concepts. Yet for 25 towns to combine, means that some groups must establish a benefit structure which will be different from what others want. Home rule for municipalities is good, but in many instances it has an expensive price tag.
>
> In the national Blue Cross–Blue Shield picture dealing with national accounts there is the same conflict between local plans and benefits on one hand and on the other a workable system which is contrary to the philosophy and practices of certain plans.
>
> In the long run Blue Cross and Blue Shield Plans must get together with some individual sacrifices — cities and towns must get together on joint programs with some loss of home rule — hospitals and Blue Cross must agree on some reasonable method of securing to hospitals the money needed to serve their patients and its subscribers.

The report ends on a somewhat somber note. Pointing out that 100,000,000 people in the United States have some form of voluntary hospital protection (more than 50,000,000 with Blue Cross), the executive director concludes, "if we cannot continue to provide this obviously necessary protection within the voluntary community framework, I fear we shall have to face the responsibility of a compulsory prepayment program."

One has, however, only to review the growth of the Blue Cross plan in Massachusetts since its inception in 1937. Its contributions to financing hospital care and its service as a bulwark against socialization of medicine are self-evident. In this time it has met and solved many problems. There is no reason to doubt that its present problems will be solved to the satisfaction of all concerned — the hospitals, the medical profession and individual subscribers.

LANCET AGAIN FULL-FLESHED

THE London *Lancet* in full flesh again with its issue of April 7 was a welcome sight after nearly two months of an appearance with little showing, perforce, but its bones. Labor difficulties with the printing craftsmen had reduced this venerable contemporary of the *Journal*, since mid-February, to a token 4-page publication providing space for little besides a periodic exhibition of the indomitable spirit of Wakley and Fox.

The *Lancet's* triumph over this latest crisis leaves it still, so far as a cursory study shows (in company with this journal), in the position of having yet to miss its weekly appearance since its establishment in 1823. In the same year the *Boston Medical Intelligencer* started its hebdomadal career, which has continued uninterruptedly, during and after its amalgamation with the *New England Journal of Medicine and Surgery*, also until the present day.

The physicians of Allegheny, Michigan, have adopted a set of rules, one of which we would like to see tried on. They mutually pledge themselves not to attend a patient unless the physician previously in attendance shall have been "regularly discharged, and satisfactorily compensated for his attendance."

Boston M. & S. J. *June 5, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

POST-PARTUM HEMORRHAGE

A thirty-three-year-old gravida III, para II, experienced a normal pregnancy, uneventful prenatal course and a normal six-hour labor. Under nitrous oxide, oxygen and ether anesthesia, after manual rotation because of a persistent occiput posterior presentation, an infant weighing 3.5 kg. (7 pounds, 14 ounces) was delivered by low forceps. The placenta was delivered within five minutes, followed by routine oxytocics, but the patient started to bleed excessively almost immediately after completion of the third

stage. Ergotrate was repeated in fifteen minutes, and although the fundus remained soft, a tight abdominal binder was applied. Shortly thereafter, further Ergotrate was given intravenously. Glucose and water were started half an hour post partum when the blood pressure and pulse were unobtainable and the face was very pale. At this time, blood typing and crossmatching were ordered. The patient's condition continued to deteriorate as further Ergotrate and dextran were given; she died one hour and forty-five minutes post partum and about forty-five minutes after blood had become available. Transfusion, however, had been withheld because all the veins were collapsed; the physician had called a consultant instead.

There was no autopsy.

This case was classified as a preventable death due to post-partum hemorrhage. The primary avoidable factor was absence of transfusion and inadequate treatment. Fifteen minutes after delivery, the fundus was described as soft, and Ergotrate was given. The record also states that an abdominal binder was applied. The selection of this utterly inadequate, ineffective and antiquated treatment was unfortunate. Bleeding of a uterus that is soft because of atony can be controlled only by direct bimanual compression, particularly if it does not respond to oxytocics. A binder not only fails to perform this function but also adds immeasurably to the hazards by completely obscuring the fundus and making it absolutely impossible for an attendant to observe its condition.

Bleeding continued, and in ten minutes Ergotrate was again given intravenously. Belatedly, crossmatching was ordered at this point, and glucose was started intravenously. These measures should have been instituted at least twenty minutes earlier when the patient was still in satisfactory condition. However, despite the fact that she was now in collapse, large amounts of blood given rapidly would undoubtedly have saved her life. The numerous difficulties inherent on obtaining blood in a hurry are recognized, and there is no objection to the use of dextran as a stopgap pending its arrival. However, it is absolutely inconceivable that twenty-five minutes later, when the blood was available, it was not given because of collapsed veins. It hardly seems necessary to point out that a cut-down on any peripheral vein and the insertion of a cannula could easily have been done. Even though personnel were undoubtedly very busy trying to institute the measures ordered, a consultant should have been called before the patient was in extremis.

These are harsh criticisms, but they are offered in a constructive spirit. Death from post-partum hemorrhage can be prevented in this day and age, certainly in Massachusetts. The probable difficulties preventing an exploration of the birth canal in a search for lacerations above the perineum are appreciated, but in view of the rotation because of a persistent occiput posterior position, vault lacerations should certainly have been sought and a repair might indeed have allowed the patient to live.

JOHN FIGGIS JEWETT, M.D.
Chairman

GENERAL COURT AND FRIENDS

The group reviewing the resolve, passed by the General Court on May 10, congratulating the Massachusetts Medical Society on the occasion of its hundred and seventy-fifth anniversary consists of, left to right: Senator Charles W. Hedges, of Quincy,

sponsor of the resolve; Senator Richard I. Furbush, of Waltham, president of the Senate; Dr. Robert W. Buck, of Waban, secretary of the Massachusetts Medical Society; Dr. Conrad Wesselhoeft, of Boston, president of the Society; and Representative Michael F. Skerry, of Medford, Speaker of the House.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1956

RÉSUMÉ

DISEASE	APR. 1956	APR. 1955	SEVEN-YEAR MEDIAN
Chancroid	1	2	2
Chicken pox	2607	2044	1826
Diphtheria	0	4	7
Dog bite	1302	1291	1291
Dysentery, bacillary	0	7	7
Encephalitis, infectious	2	2	4
German measles	977	599	599
Gonorrhea	107	137	162
Granuloma inguinale	0	0	0
Hepatitis, infectious	25	98	13
Lymphogranuloma venereum	0	0	0
Malaria	0	0	0
Measles	512	6124	2022
Meningitis, meningococcal	3	4	6
Meningitis, Pfeiffer bacillus	2	6	6
Meningitis, pneumococcal	1	1	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	4	6	5
Mumps	389	1314	1346
Poliomyelitis	1	2	0
Salmonellosis	37	24	7
Scarlet fever	705	1146	601
Syphilis	163	195	136
Trichinosis	1	0	1
Tuberculosis, pulmonary	146	158	198
Tuberculosis, other forms	5	5	12
Typhoid fever	0	2	2
Undulant fever	1	0	1
Whooping cough	72	139	171

Comment

Diseases below the seven-year median were diphtheria, bacillary dysentery, measles, mumps, typhoid fever and whooping cough.

For the first time in the history of the State no cases of diphtheria or typhoid fever were reported during the month of April.

During April, whooping cough was at the lowest level for this month in the history of the State.

Mumps was the lowest level for the month of April since 1925.

With but one exception (1953) measles was at the lowest level for the month of April in the State's history.

Diseases above the seven-year median were chicken pox, German measles, infectious hepatitis, salmonellosis and scarlet fever.

Although above the seven-year median, the reported incidence of infectious hepatitis has been at a relatively low level for several months.

During April, salmonellosis was at the highest level for this month since 1943.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Encephalitis, infectious: Norton, 1; Orleans, 1; total, 2.

Hepatitis, infectious: Andover, 1; Auburn, 1; Belchertown, 1; Boston, 3; East Longmeadow, 1; Fall River, 2; Franklin, 2; Georgetown, 1; Haverhill, 1; Lowell, 2; Malden, 1; Methuen, 1; Springfield, 1; Tewksbury, 2; Weston, 1; West Springfield, 1; Westboro, 2; Worcester, 1; total, 25.

Lymphocytic choriomeningitis: Lunenburg, 1.

Meningitis, meningococcal: Framingham, 1; Holyoke, 1; Springfield, 1; total, 3.

Meningitis, Pfeiffer bacillus: Chicopee, 1; Wenham, 1; total, 2.

Meningitis, pneumococcal: Boston, 1.

Meningitis, mumps: Springfield, 1.

Meningitis, undetermined: Revere, 1; Springfield, 1; Walpole, 1; Ware, 1; total, 4.

Poliomyelitis: Pittsfield, 1.

Psittacosis: Adams, 1.

Salmonellosis: Ashland, 2; Boston, 2; Cambridge, 5; Framingham, 3; Gloucester, 3; Greenfield, 3; Hingham, 1; Hopkinton, 2; Lowell, 1; Lynn, 2; Medford, 2; Needham, 1; North Reading, 1; Plymouth, 1; Somerset, 1; Springfield, 1; Taunton, 1; Templeton, 1; West Boylston, 1; Weymouth, 1; Wilbraham, 1; Wilmington, 1; total, 37.

Trichinosis: Gloucester, 1.

Undulant fever: Springfield, 1.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Lowell	June 1	Albert H. Brewster, M.D.
Salem	June 4	Paul W. Hugenberger, M.D.
Haverhill	June 6	William T. Green, M.D., and Henry Banks, M.D.
Greenfield	June 7	Charles L. Sturdevant, M.D.
Brockton	June 7	George W. Van Gorder, M.D.
Worcester	June 8	John W. O'Meara, M.D.
Gardner	June 11	Carter R. Rowe, M.D.
Lynn*	June 11	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Hyannis	June 14	Paul L. Norton, M.D.
Springfield	June 19	James D. Fisher, M.D.
Fall River	June 25	David S. Grice, M.D.
Pittsfield	June 27	Edward J. Coughlin, Jr., M.D.

Rheumatic-Fever Clinic	Dates
North Reading	June 1, 8, 15, 22, 29
Fitchburg	June 2, 9, 16, 23, 30

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D., and Joseph E. Murray, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

REGARDING ALCOHOLISM

To the Editor: It might have escaped the attention of some physicians that at last there is a bill before the House and Senate Interstate Committee (Hon. J. Percy Priest and Hon. Warren G. Magnuson, chairmen) that will effectively strike at the evil of alcoholism by prohibiting advertising of alcoholic beverages on television, radio and in magazines.

The *Journal* has devoted space within the last year to the study and treatment of this malady and its consequences, but the hopelessness of adequate cure and rehabilitation is obvious even to the most sanguine observer. Most students of alcoholism agree that the habit is formed in early years when some sort of a "maturation" ritual takes place in the mind of the young man who joins the fraternity of "the boys," gulping down his first glass of beer or whiskey. Whenever there is a gathering of men thereafter, the hypnotic, repetitive voice of paid advertisements is somewhere in the background of their minds, reiterating "beer belongs, whiskey is distinguished, moderation does not hurt." As in Huxley's novel, *Brave New World,* these catch phrases have become part and parcel of everybody's thought, and to displace them the medical profession, as well as the law and the clergy, has been struggling in vain. The added hypnotic force of television is making such subtle suggestions almost irresistible.

Every guardian of the people's health should write to these congressional leaders at once and demand that the bill be voted out of committee favorably.

George Vash, M.D.

Chicopee Falls, Massachusetts

RELATIVELY SPEAKING

To the Editor: Congratulations to the authors of "The Artist's Template," which appeared in the April 26 issue of the *Journal.* Drs. Lentino and Rubenfeld have made a small effort but a worthy one. As a contribution to the science of medicine, the general attainment of objectivity in clinical description would rank with the development of the residency system.

I see one flaw in the template illustrated. It is calibrated in fractions of the inch. Case reports using such measurements must inevitably appear in some journal that sticks firmly to the metric system. Thereupon the 5/32-inch lesion will wind up as "0.408 cm." This is the same journal that translates "approximately 1-1½ inches" to read "25.4-38.1 mm." The editor who makes this change is of the same school as the staff of the newspaper that prints an archeologist's statement "worth 500,000 pounds" to read "estimated value $1.4 million." It is unfortunate that the newspaper fails to appreciate the significance of the rise in the pound to $2.81. What the paper really meant was "$1,405,000."

Bellevue and Montefiore hospitals are fortunate in having staffs that (apparently) are accustomed to the use of the ruler, although inaccurately. This in itself is a great advance over the best-fit-to-available-still-life method. To get a true picture of a tumor "the size of an orange" one must know whether the patient was seen in Miami, Los Angeles, Brownsville or New Orleans. Still further, the date of the

observation is pertinent. It is my impression (unconfirmed) that the mean size of the fruit of *Citrus sinensis* has changed somewhat since the days when I was a grocery clerk.

It will be a great day when we can dispose of the last millet seed.

DOUGLAS LINDSEY, M.D.

Lacassine, Louisiana

RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held May 10, 1956, it was voted to restore the registration of Dr. Luis A. Mendoza, 104 Coolidge Street, Brookline, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEWS

The Biologic Effects of Tobacco: With emphasis on the clinical and experimental aspects. Edited by Ernest L. Wynder, M.D. With a foreword by Joseph Garland, M.D. 8°, cloth, 215 pp., with 20 illustrations and 7 tables. Boston: Little, Brown and Company, 1955. $4.50.

This volume will be most salutary to those whose aim it is to restore to tobacco smoking all of its virtues—fragrance, sedation, meditation, stimulation—and rid it of its hazards—thromboangiitis obliterans, gastric irritation, cardiovascular crises, and cancer. Of particular value to future researchers are chapters on the chemistry of the plant, the physics of combustion and distillation of the fragrant leaf and pharmacologic properties of tobacco and tobacco smoke. All of this is so vivid that it is perhaps best not to read about the effects of nicotine on the central nervous system, or the cardiovascular system while smoking. The chapters of most interest to practitioners are on the cardiovascular system—"nicotine is the most noxious agent"; cancer—"smoking . . . plays a role in the causation of lung cancer"; the gastrointestinal tract—"control of the use of tobacco is essential for proper medical management"; and allergy which "is of the same type as that seen in pollenosis, often referred to as atopy."

A last chapter by E. Cuyler Hammond on cause and effect seems rather ponderous by comparison with this previously published field study. In it epidemiologic research is discussed largely in the abstract: "the problem is to discover causative factors which increase the probability of human disease or death and are operative and important under various conditions of human life which occur with appreciable frequency." This chapter is directed at a research audience but the reader wonders why it isn't given over more largely to Hammond's own thoughts on Hammond and Horn's own studies. Why discuss epidemiology as a field in the last chapter and not chemistry or pharmacology as disciplines, in the first two? Perhaps the reason is because Wynder's chapter on neoplastic diseases is in the main a presentation of the epidemiology of lung cancer in relation to smoking. It draws heavily on the work of Wynder. Why the important data of Breslow and his associates is merely alluded to by a reference number is a mystery to this reviewer.

When all the smoke has cleared away the burning questions remain: to smoke or not to smoke, to inhale or not to inhale, to smoke with asbestos filters or with no filters at all. Whatever the decisions, the authors are agreed that there is a risk to habitual smoking. As Garland puts it in his foreword, "Some (indulgences) seem to be practically without danger, like chewing gum and playing the ocarina. Others have varying elements of risk . . ." What to do about smoking, however, is left to some unsung genius of the future who will probably be operating more with the first two chapters than the last five. Therein are discussed the half dozen or more ketones, nearly twenty acids and all sorts of alcohols and phenols, not to mention alkaloids, hydrocarbons, miscellaneous organic compounds and a host of inorganic compounds including just about all of the metals; the unsung genius will have his work cut out for him. Meanwhile, if physician or patient is weak willed and still wants to smoke moderately and inhale, he can, of course, smoke filter tips but since filter efficiency depends "primarily on inertial deposition to cause a partial precipitation of the smoke particulates" he may not enjoy the filtrate. Smoke bereft of its particles is a pale shadow of the pungent wisps that Sir Walter Raleigh is said to have introduced to the Western World. However, according to this little volume, there is probably no truth in the old tale that he was doused with ale for his temerity.

As for clinical usefulness of the brochure it is problematical. The clinician is finally told, "it seems clear that a moderation of smoking habits is indicated"; but the concept of moderation is not new; it remains unquantitated. The smoking physician will recognize much of what he has been telling his patients (and himself) for many years. The nonsmoker too will appreciate that he has been right all along and hence will not need to read the book.

T. H. INGALLS, M.D.

A Doctor's Book of Hours: Including some dimensions of the emotions. By Merrill Moore, M.D. 8°, cloth, 397 pp. Springfield, Illinois: Charles C Thomas, 1955. $6.00.

This Book of Hours, by Boston medicine's most indefatigably articulate writer since Oliver Wendell Holmes, would have been more appropriately titled "A Book of Days," since that is the actual division of the material. We are given one sonnet for each of the days of the year; though the arrangement is not seasonal — that is to say, a sonnet assigned to October might just as well have been given to any other month or any other date — it is far from being haphazard. There is a design in the book, even a clinical design, for though the patient happens to be abnormally overweight and desperately intractable, being none other than Mr. Anthropos himself, the record of his examination is as orderly as it is painstaking. His disease is simply the disease of being himself, which is incurable, but Dr. Moore, whose apparently casual notations reveal the philosopher as much as the poet, does more than record. His verse at its best casts the queer sort of shadow that each of us recognizes as being in some respects his own; it enforces, or reinforces, self-awareness, which I take to be one of the more important functions of art. Considered individually, many of these sonnets could be dismissed as cranky, or trite, or unfocused, or simply as being too trivially occasional to stand, but the weakest of them have their place in the design, and without them the book would not have the fine human conviction that distinguishes it from ordinary hit-and-run observation. It is the work of a specialist; yet it is not for specialists other than those of human behavior — and that means all of us. Least of all, I think, is it a work for literary men. Dr. Moore is a writer, but his poetry is lived, not written — or, better, written with the immediacy of living.

The shortcomings of this kind of thing are implicit in the design. One imagines that any clinical record must have its *longueurs*, its perfunctory elaborations and recapitulations, over which even the most devoted specialist will nod. These lapses are inevitable, but Dr. Moore is so intent upon progressing, so impatient of craftsmanship, that his lapses are much more downright than they need be, verging too often upon a kind of prattling naïveté. He is, moreover, less daring, less experimental than he was in his earlier books. It is almost as though, having salvaged the sonnet form from respectability by sheer force of character, — and this, I think, is an accurate judgment, — he had decided now to let it coast. But coasting, beautiful coasting, is precisely what brought the form into disrepute in the first place, and it would be a pity if one kind of respectability had been discredited merely in favor of another kind. As the freshness wears off (and it must), the devices of conscious technic become more and more imperative, but Dr. Moore has never seemed particularly aware of this necessity, and there is little indication that he will become so. One apprehends, then, a

formula — curiously, a formula of nonformulation — that works now, that works for the present. Maybe that is enough. Certainly, it is engaging. But it deserves a greater extension than the *Book of Hours* suggests.

In the meantime, these are literary preoccupations, and the book is a living fact. I cannot imagine anyone's failing to be held by some aspect of it, and the reflective will find much more here than the informal design seems to promise.

DUDLEY FITTS

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Hypertension: A manual for patients with high blood pressure. By Irvine H. Page, M.D., director, Research Division, Cleveland Clinic Foundation, and president of the American Heart Association, Cleveland. Second edition. 12°, cloth, 109 pp., with 7 illustrations. Springfield, Illinois: Charles C Thomas, 1956. $3.00.

Tabulae haematologicae. By Prof. Dr. med. Karl Rohr, Zürich. 8°, paper, 68 pp., with 16 colored charts by L. Bollinger-Schudel, Zürich. Stuttgart: Georg Thieme, 1956. DM 8.40. $2.00. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Poliomyelitis Vaccination: A preliminary review. 8°, paper, 40 pp., with illustrations and tables. Geneva: World Health Organization, 1956. Price 1/9., Sw. fr. 1.-, $0.30. Also available in French and Spanish. (*Technical Report Series*, No. 101.) (Distributed by Columbia University Press, New York City.)

The Inquisitive Physician: The life and times of George Richards Minot, A.B., M.D., D.Sc. By Francis M. Rackemann, M.D. 8°, cloth, 288 pp., with a frontispiece. Cambridge, Massachusetts: Harvard University Press, 1956. $5.00.

Operative Technic in Specialty Surgery. Edited by Warren H. Cole, M.D., professor of surgery and head, Department of Surgery, University of Illinois College of Medicine, and chief surgeon, Illinois Research and Educational Hospitals, Chicago. With 67 contributing authors. Introduction by Allen O. Whipple. Second edition. 8°, cloth, 967 pp., with illustrations and tables. New York: Appleton-Century-Crofts, Incorporated, 1956. $20.00.

Allergy in Childhood. By Jerome Glaser, M.D., assistant professor of pediatrics, University of Rochester School of Medicine and Dentistry, pediatrician-in-chief, Genesee Hospital, consulting pediatrician, Rochester General and St. Mary's hospitals, Rochester, New York, regional consultant, Jewish National Home for Asthmatic Children, Denver, Colorado, and chairman of the Section on Allergy of the American Academy of Pediatrics. 8°, cloth, 529 pp., with 42 illustrations and 39 tables. Springfield, Illinois: Charles C Thomas, 1956. $12.50. (Publication No. 272, *American Lecture Series.*)

Modern Operative Surgery. Edited by the late G. Grey Turner, LL.D., D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., professor of surgery in the University of London, director, Department of Surgery, British Postgraduate Medical School, and surgeon, Hammersmith Hospital; and Lambert Charles Rogers, V.R.D., M.Sc., M.D., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S., professor of surgery, University of Wales, director of Surgical Unit, Cardiff Royal Infirmary, surgeon, United Cardiff Hospitals, adviser in surgery, Welsh Regional Hospital Board, and consultant in neurosurgery to the Royal Navy. With a foreword by Sir Gordon Gordon-Taylor, K.B.E., C.B., M.A., LL.D., Sc.D., M.D., M.S., F.R.C.S., F.R.C.S.E., F.R.C.S.I., F.R.A.C.S., F.A.C.S. Fourth edition. 8°, cloth, 1229 pp., with 476 illustrations. New York: Harper and Brothers, 1956. $15.00.

Clinical Laboratory Diagnosis. By Samuel A. Levinson, M.S., M.D., Ph.D., director of laboratories, University of Illinois Research and Educational Hospitals, Chicago, and professor of pathology, University of Illinois College of Medicine; and Robert P. MacFate, Ch.E., M.S., Ph.D., chief, Division of Laboratories, Board of Health, City of Chicago, director of laboratories, Municipal Contagious Disease Hospital, Chicago, director of laboratories, Municipal Social Hygiene Clinic, Chicago, and senior scientist(R), United States Public Health Service. Fifth edition, thoroughly revised. 8°, cloth, 1246 pp., with 244 illustrations, 142 tables and 13 plates, 11 in color. Philadelphia: Lea and Febiger, 1956. $12.50.

NOTICES

MEDICAL LIBRARY ASSOCIATION

The fifty-fifth annual meeting of the Medical Library Association will be held at the Hotel Statler, Los Angeles, June 18-22. Preconvention activities will begin on Sunday, June 17. The theme of the program will be "Medicine Moves West." Further information may be obtained from Mrs. Ella Crandall, Librarian, Los Angeles County General Hospital, 1200 North State Street, Los Angeles 33, California.

AMERICAN PHYSICIANS FELLOWSHIP COMMITTEE OF ISRAEL MEDICAL ASSOCIATION

The Annual Assembly and Banquet of the American Physicians Fellowship Committee of the Israel Medical Association will be held during the American Medical Association convention, at the Hotel Morrison, Chicago, on Monday, June 11.

The guest of honor will be Dr. Moshe Sherman, president of the Israel Medical Association. The main speaker will be Dr. George J. Mohr, of Chicago, who will discuss "Some Medical Perspectives in Israel–Personal Observations." Further information may be obtained from the American Physicians Fellowship Committee of the Israel Medical Association, 1330 Beacon Street, Brookline 46, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.

JUNE 1. Massachusetts Society of Anesthesiologists. Page 968, issue of May 17.

JUNE 1–9. International Medical-Surgical Meetings. Page 540, issue of March 15.

JUNE 4–6. Third National Cancer Conference. Page 876, issue of May 3.

JUNE 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

JUNE 6–10. American College of Chest Physicians. Page 876, issue of May 3.

JUNE 7. New England Hospital Staff Clinical Conference. Page 968, issue of May 17.

JUNE 9 and 10. Society for Investigative Dermatology. Page 876, issue of May 3.

JUNE 10 and 11. American Gastroscopic Society. Page 875, issue of May 3.

JUNE 11. American Physicians Fellowship Committee of Israel Medical Association. Notice above.

JUNE 15. New England Pediatric Society. Page 924, issue of May 10.

JUNE 17. American Electroencephalographic Society. Page 924, issue of May 10.
JUNE 18–20. American Neurological Association. Page 875, issue of May 3.
JUNE 18–22. Medical Library Association. Page 1051.
JUNE 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
JUNE 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.
JULY 9. Fifth Annual Symposium for General Practitioners. Page 1010, issue of May 24.
AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 7

THURSDAY, JUNE 7
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Immunological Studies in Relation to Mitral Valve Surgery. Dr. Joseph M. Miller. Main Amphitheater, Peter Bent Brigham Hospital.
*8:00 p.m. New England Hospital Staff Clinical Conference. Nurses' Home, New England Hospital, Roxbury.

FRIDAY, JUNE 8
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Pratt Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, JUNE 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JUNE 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Medical Conference. Stearns Auditorium. New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Stellate-Ganglion Nerve Block. Dr. Vandam. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon and staff. Stearns Auditorium, New England Center Hospital.

TUESDAY, JUNE 12
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00–1:00 p.m. Endocrine Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–2:00 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Ettsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, JUNE 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. A Family Affair (motion picture). Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery, and Psychiatry Conference. Drs. Bertram Selverstone, John F. Sullivan and Justin Hope. Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Auditorium, New England Center Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:00 p.m. Surgical Pathology Conference. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.